PARP Inhibition in the Management of Prostate Cancer — Where We Are and Where We're Headed

Thursday, June 23, 2022
5:00 PM – 6:00 PM ET

Faculty

Johann S de Bono, MB ChB, MSc, PhD, FMedSci
Fred Saad, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Johann S de Bono, MB ChB, MSc, PhD, FMedSci
Regius Professor of Cancer Research
Professor of Experimental Cancer Medicine and
Honorary Consultant in Medical Oncology
Head of Clinical Studies Division
Director of Drug Development Unit
Head of the Prostate Cancer Targeted Therapy Group
The Institute of Cancer Research and
The Royal Marsden NHS Foundation Trust
London, United Kingdom

Fred Saad, MD
Professor and Chief of Urology
Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center (CHUM)
Director, Prostate Cancer Research
Montreal Cancer Institute/CRCHUM
Montréal, Québec, Canada

MODERATOR
Neil Love, MD
Research To Practice

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP and Merck.

Dr Love — Disclosures

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Prof de Bono — Disclosures

No relevant conflicts of interest to disclose

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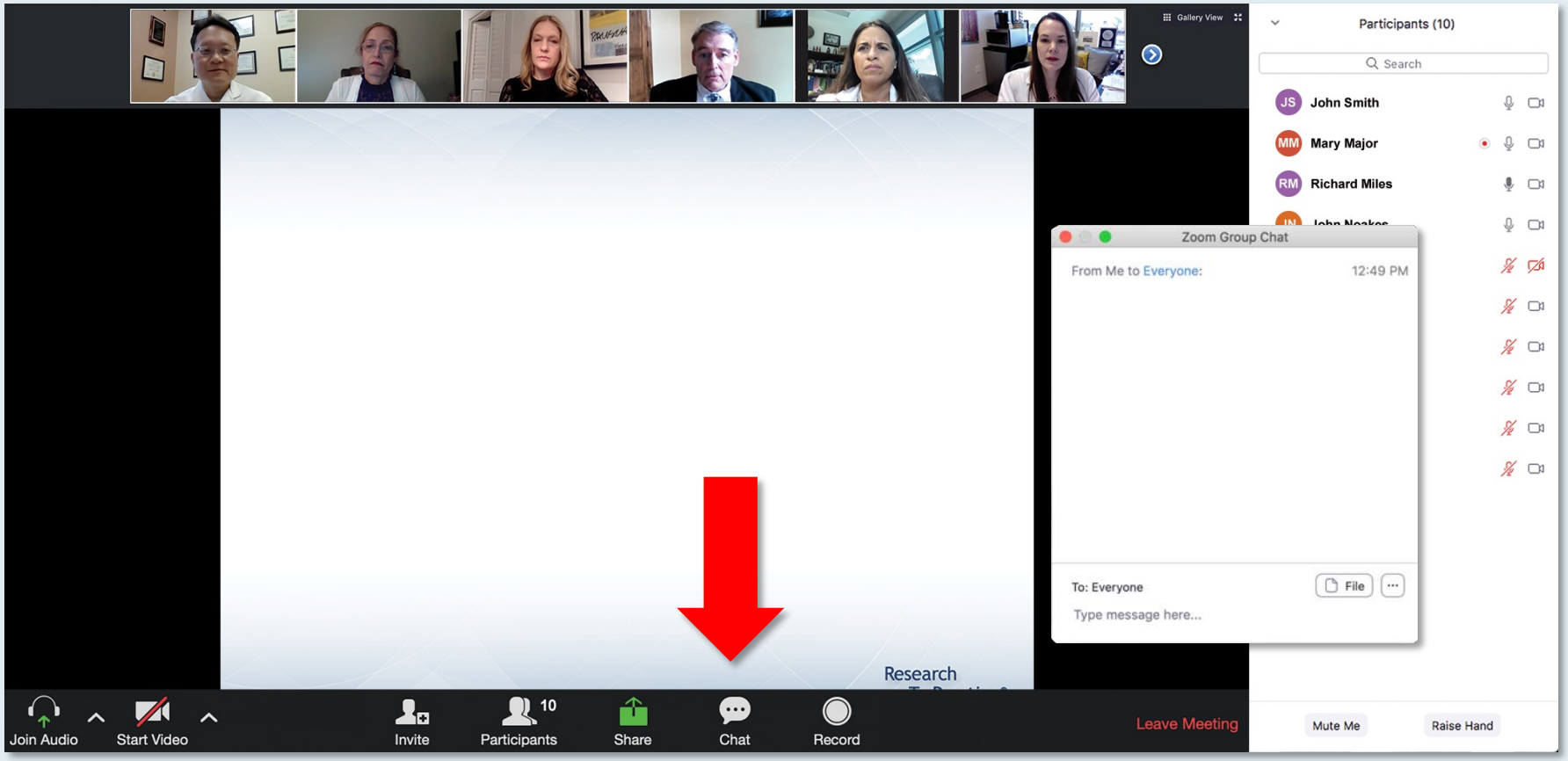
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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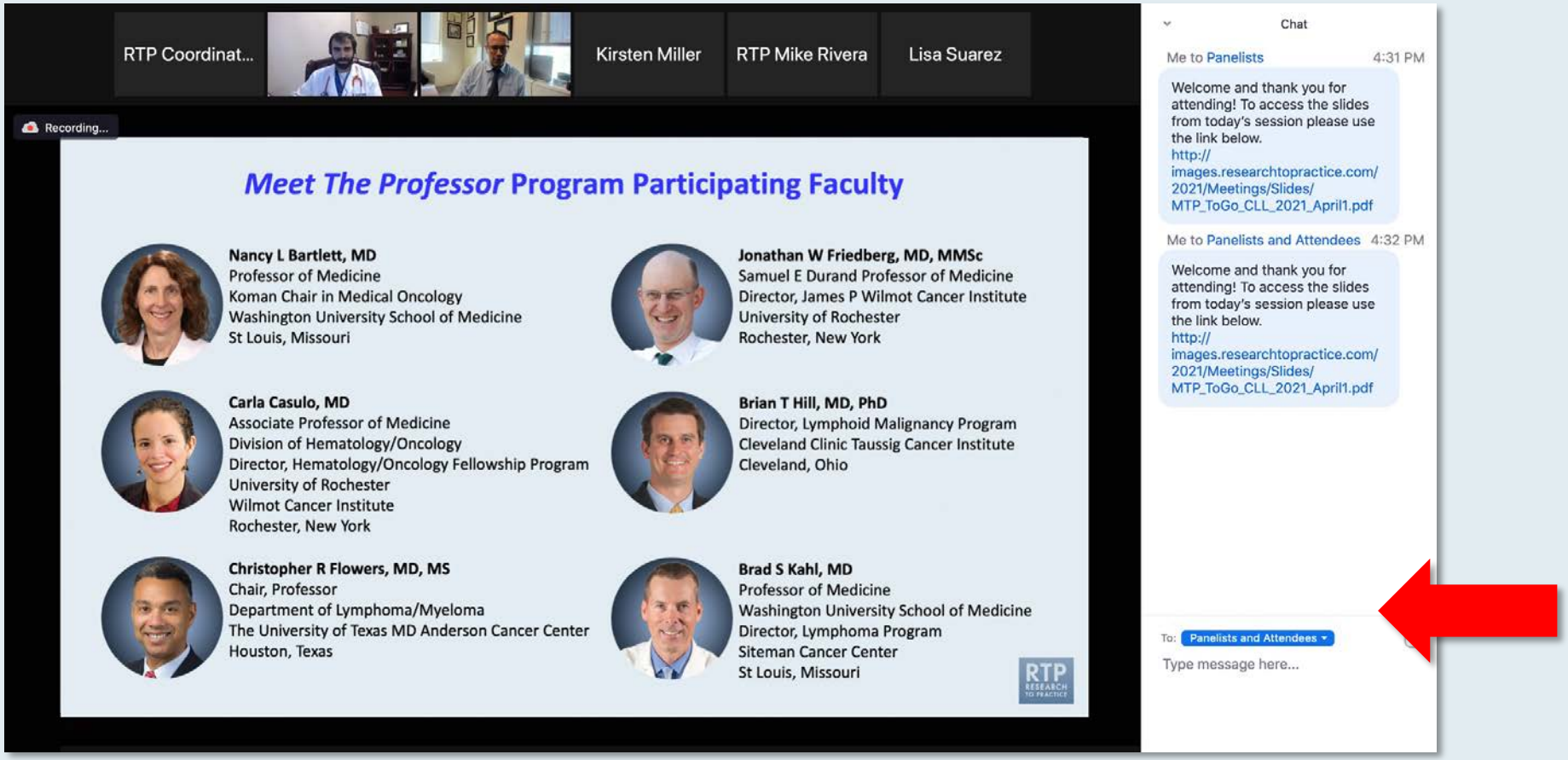
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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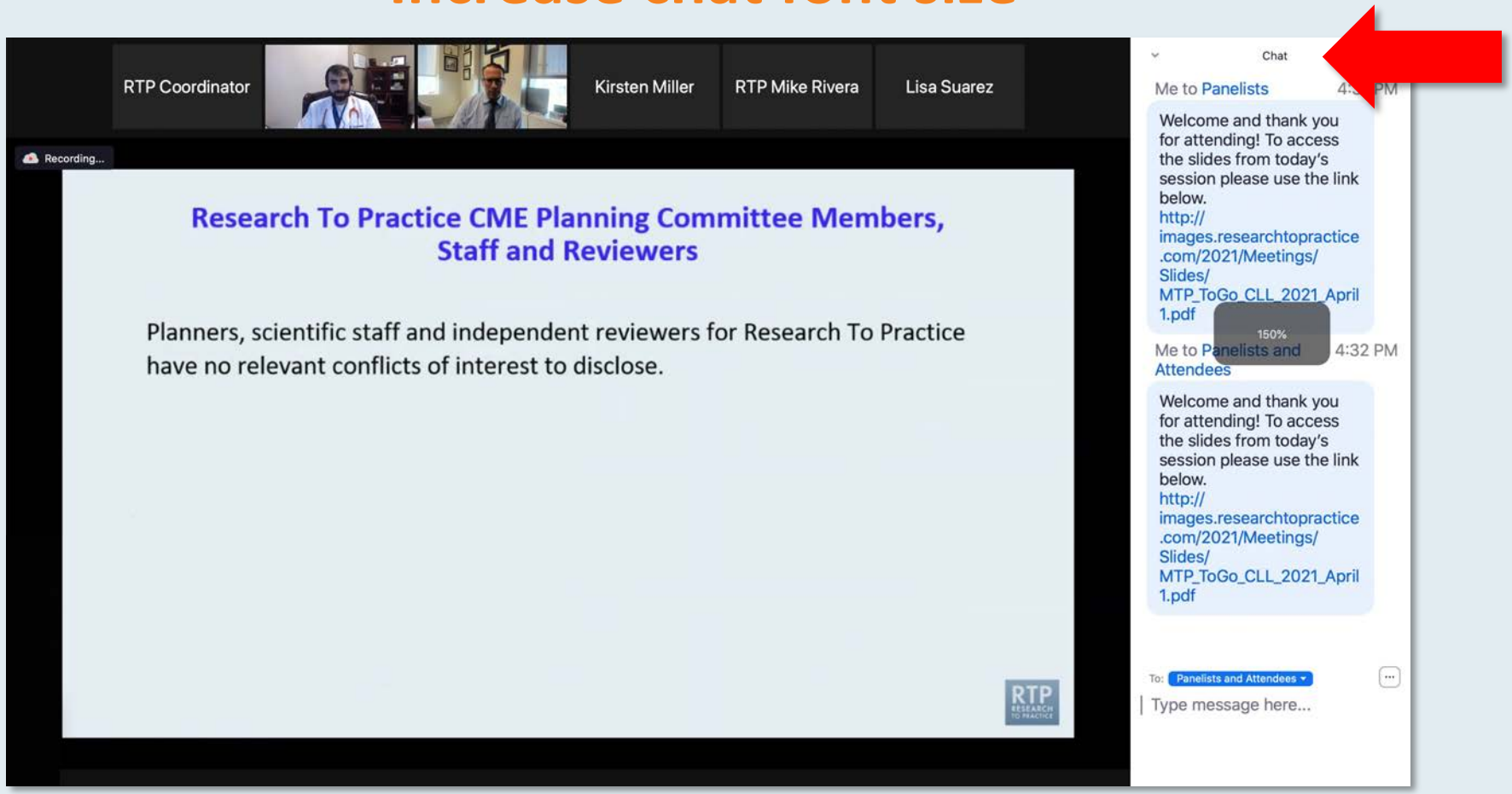

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Novel Agents and Strategies for the Treatment of Metastatic Castration-Resistant Prostate Cancer

DR EVAN YU

FRED HUTCHINSON CANCER RESEARCH CENTER

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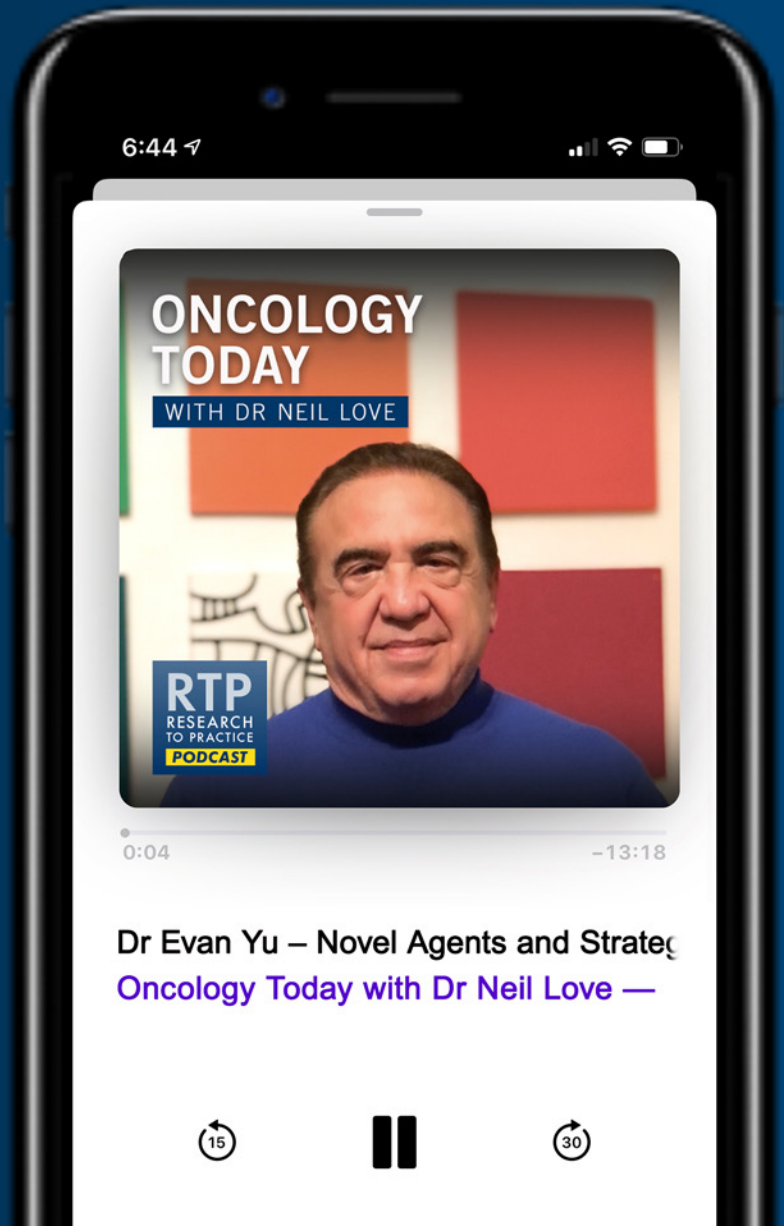

Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, June 28, 2022
5:00 PM – 6:00 PM ET

Faculty

Jorge E Cortes, MD

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Non-Small Cell Lung Cancer with an EGFR Mutation

Thursday, June 30, 2022
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD

Moderator

Neil Love, MD

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TO PRACTICE

Meet The Professor

Optimizing the Management of Ovarian Cancer

Wednesday, July 6, 2022
5:00 PM – 6:00 PM ET

Faculty

Ursula Matulonis, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Hepatobiliary Cancers

Thursday, July 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Tuesday, July 12, 2022
5:00 PM – 6:00 PM ET

Faculty

Samuel J Klempner, MD

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Neil Love, MD

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Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes – A Review of the 2022 ASCO Annual Meeting and EHA Congress

Wednesday, July 13, 2022
5:00 PM – 6:00 PM ET

Faculty

Richard M Stone, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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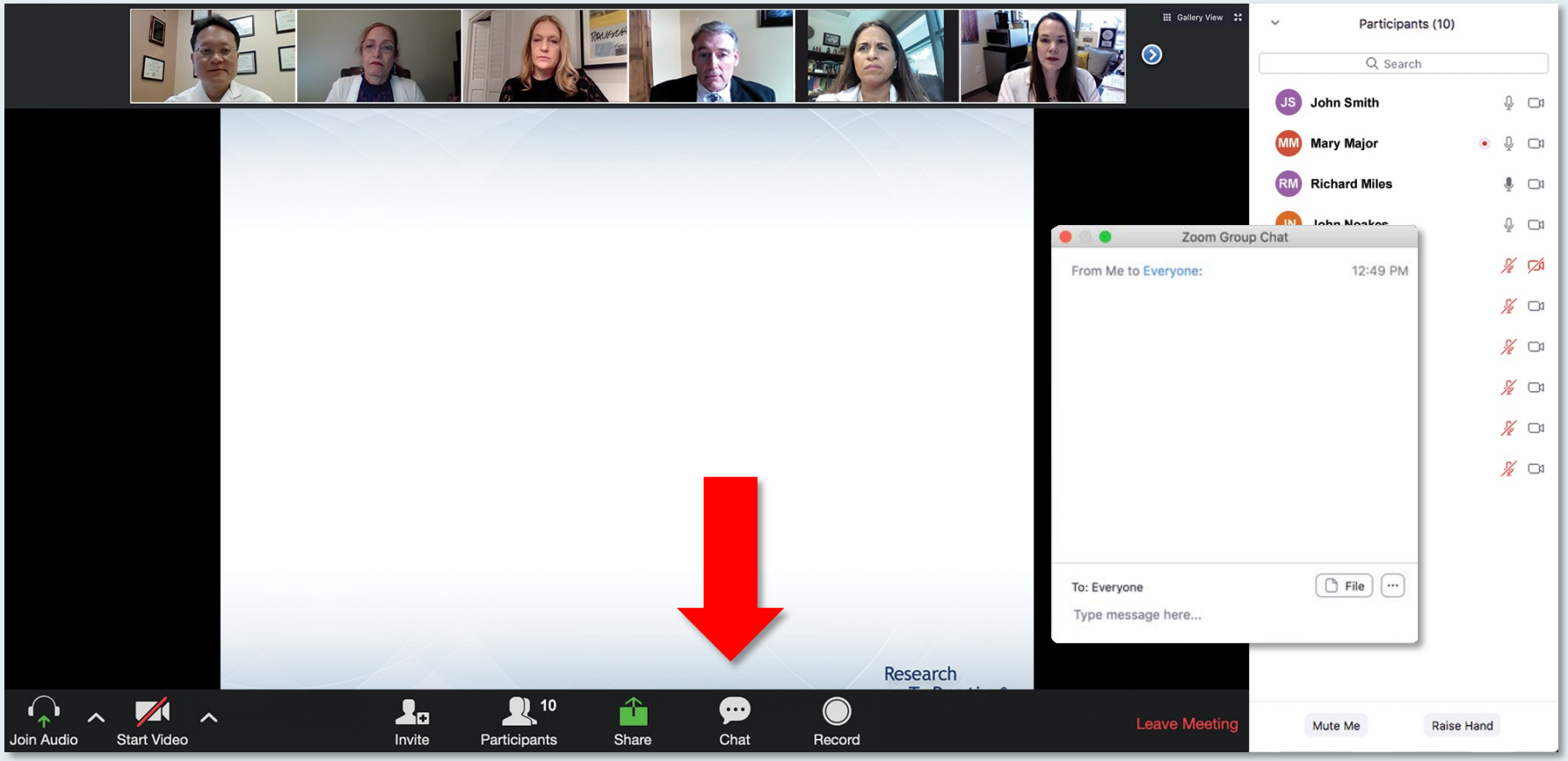

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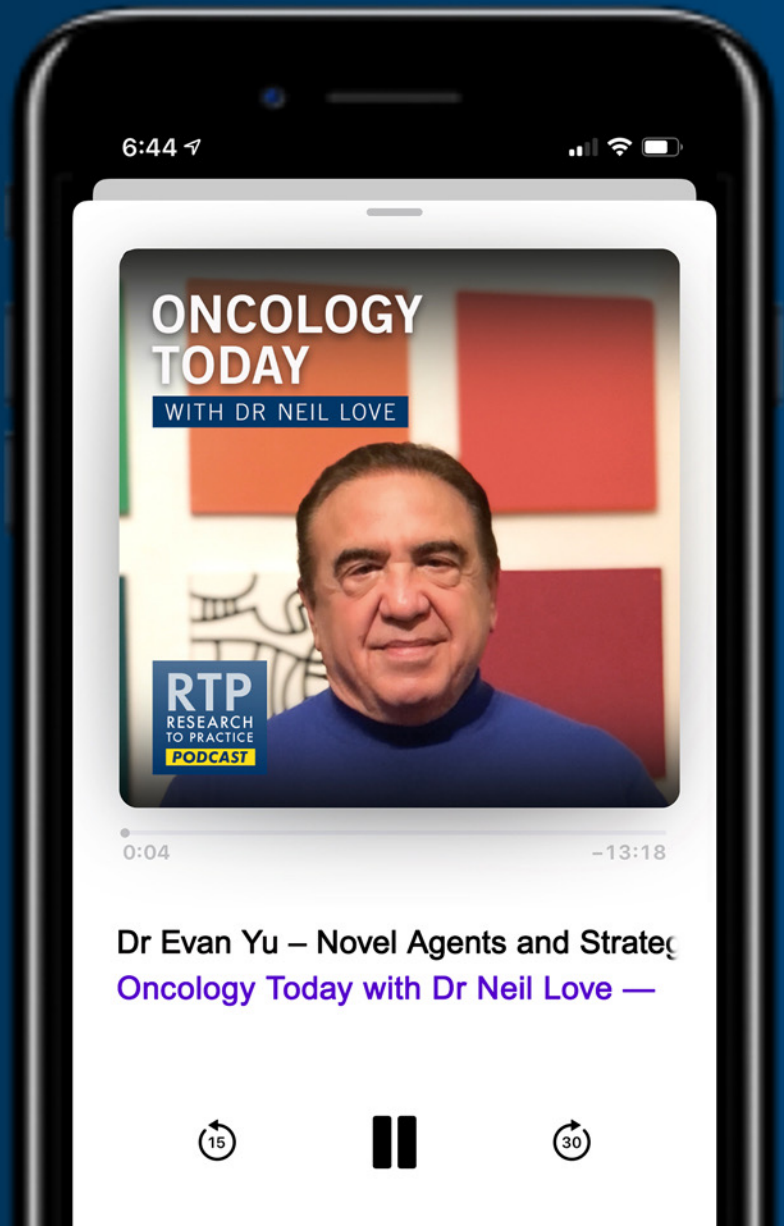

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PARP inhibition for Prostate Cancer

Johann Sebastian de Bono

Regius Professor, Head of the Drug Development Unit,
The Institute of Cancer Research and Royal Marsden Hospital,
London, United Kingdom

Opening the door for PARPi treatment: What lies ahead?

Fred Saad MD FRCS

Professor and Chairman of Urology
Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center
Montreal, QC, Canada

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Dabrafenib/Trametinib Combination Granted Accelerated Approval for a Tumor-Agnostic Indication for Solid Tumors with BRAF V600E Mutations

Press Release – June 23, 2022

"…the US Food and Drug Administration (FDA) granted accelerated approval for dabrafenib + trametinib for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. In accordance with the Accelerated Approval Program, continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The FDA approval was based on clinical efficacy and safety demonstrated in three clinical trials. In the Phase II ROAR (Rare Oncology Agnostic Research) basket study and the NCI-MATCH Subprotocol H study, dabrafenib + trametinib resulted in overall response rates of up to 80% in patients with BRAF V600E solid tumors, including high- and low-grade glioma, biliary tract cancer and certain gynecological and gastrointestinal cancers. An additional study (Study X2101) demonstrated the clinical benefit and acceptable safety profile of dabrafenib + trametinib in pediatric patients.

The safety profile of dabrafenib + trametinib observed in these studies was consistent with the known safety profile in other approved indications."

https://www.novartis.com/news/media-releases/novartis-tafinlar-mekinist-receives-fda-approval-first-tumor-agnostic-indication-braf-v600e-solid-tumors

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Introduction: This Week on RTP

MODULE 1: PARP Inhibitors in Prostate Cancer – Top 10 List

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Meet The Professor
Optimizing the Management of Ovarian Cancer

Shannon N Westin, MD, MPH
Associate Professor
Director, Early Drug Development
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

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original reports

A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45)

Bradley J. Monk, MD[1]; Christine Parkinson, MD[2]; Myong Cheol Lim, MD, PhD[3]; David M. O'Malley, MD[4]; Ana Oaknin, MD, PhD[5]; Michelle K. Wilson, MD[6]; Robert L. Coleman, MD[7]; Domenica Lorusso, MD, PhD[8]; Paul Bessette, MD[9]; Sharad Ghamande, MD[10]; Athina Christopoulou, MD, PhD[11]; Diane Provencher, MD[12]; Emily Prendergast, MD[13]; Fuat Demirkiran, MD[14]; Olga Mikheeva, MD[15]; Oladapo Yeku, MD, PhD[16]; Anita Chudecka-Glaz, MD, PhD[17]; Michael Schenker, MD, PhD[18]; Ramey D. Littell, MD[19]; Tamar Safra, MD[20]; Hung-Hsueh Chou, MD[21,22]; Mark A. Morgan, MD[23]; Vít Drochýtek, MD[24]; Joyce N. Barlin, MD[25]; Toon Van Gorp, MD[26]; Fred Ueland, MD[27]; Gabriel Lindahl, MD[28,29]; Charles Anderson, MD[30]; Dearbhaile C. Collins, MBBCh, MA, PhD[31]; Kathleen Moore, MD[32]; Frederik Marme, MD, PhD[33]; Shannon N. Westin, MD, MPH[34]; Iain A. McNeish, MD, PhD[35]; Danny Shih, BA[36]; Kevin K. Lin, PhD[37]; Sandra Goble, MS[38]; Stephanie Hume, PhD[39]; Keiichi Fujiwara, MD, PhD[40]; and Rebecca S. Kristeleit, MD, PhD[41]

J Clin Oncol 2022;[Online ahead of print].

FDA Advises Manufacturer Not to Submit First-Line Maintenance sNDA for Rucaparib Until OS Survival Data from the ATHENA-MONO Trial Are More Mature

June 17, 2022

"In consultation with the FDA, [the manufacturer of rucaparib] recently was advised not to file a supplemental new drug application based on data from a cohort of the Phase III ATHENA study until the study's overall survival data mature.

In the 8-K, [the manufacturer] said the FDA has accepted a request for a pre-NDA meeting and noted that the ATHENA-MONO portion of the Phase III study has met its primary endpoint of progression-free survival compared to placebo. OS is a secondary endpoint for ATHENA-MONO and the data are approximately 25% mature at present. [The manufacturer] said the FDA urged it to hold off filing for supplemental approval until the OS data reach 50% maturity, and indicated an advisory committee review would likely be necessary if the data were filed earlier than that point.

In a statement to *Scrip*, the firm said that although it cannot anticipate the outcome of the pre-NDA meeting, 'we are encouraged that the FDA is willing to have a dialogue.' [They] estimate the ATHENA-MONO OS data will reach 50% maturity in approximately two years."

https://scrip.pharmaintelligence.informa.com/SC146575/Clovis-Withdraws-Rubraca-Ovarian-Cancer-Indication-Due-To-Survival-Imbalance?vid=Pharma

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Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Eric Van Cutsem, MD, PhD
Professor of Medicine
Digestive Oncology
University Hospitals Leuven
Leuven, Belgium

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Oncologist 2021;26(3):e414-24.

The Oncologist®

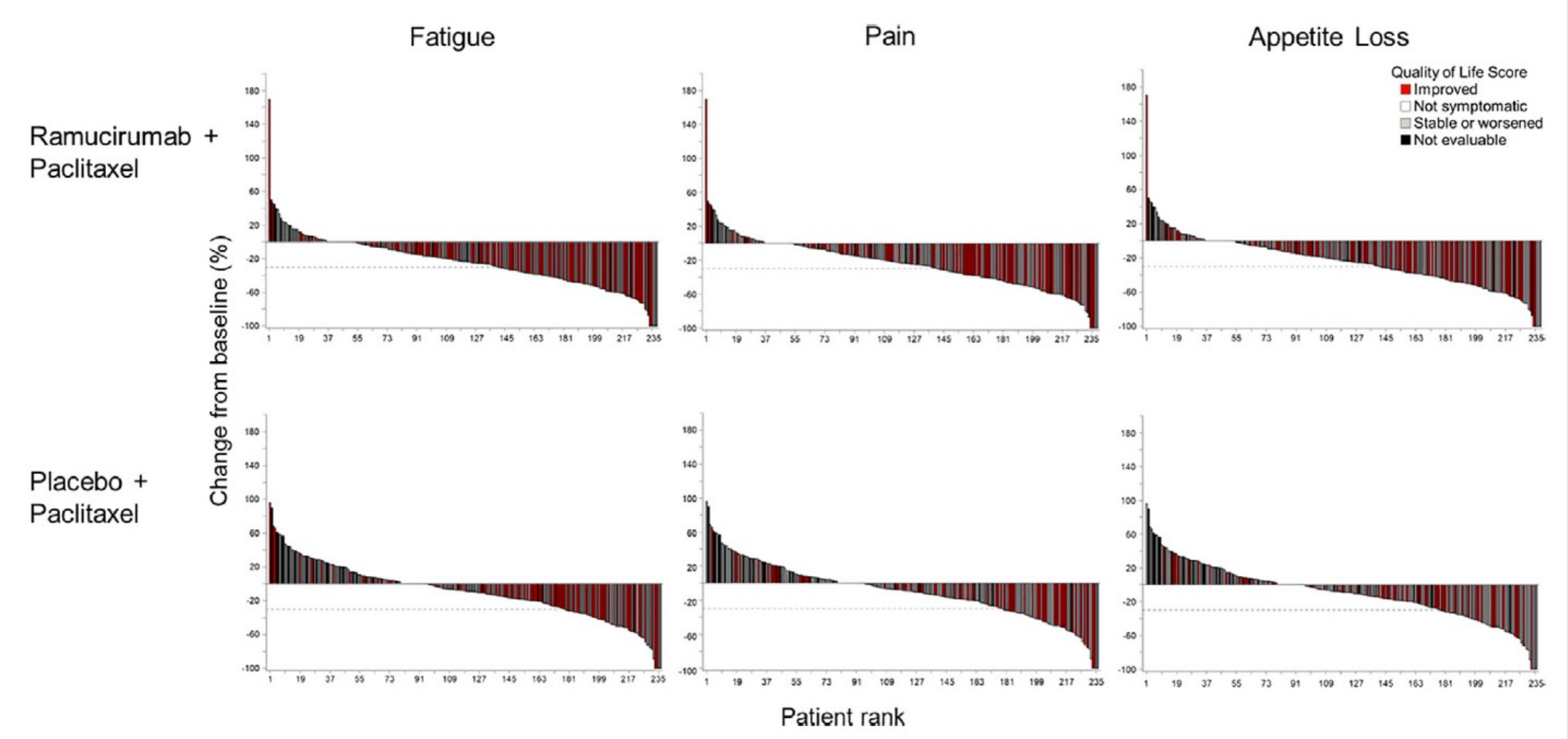
Gastrointestinal Cancer

Tumor Response and Symptom Palliation from RAINBOW, a Phase III Trial of Ramucirumab Plus Paclitaxel in Previously Treated Advanced Gastric Cancer

Stefano Cascinu,[a] György Bodoky,[b] Kei Muro,[c] Eric Van Cutsem,[d] Sang Cheul Oh,[e] Gunnar Folprecht,[f] Sumitra Ananda,[g] Gustavo Girotto,[h] Zev A. Wainberg,[i] Maria Luisa Limon Miron,[j] Jaffer Ajani,[k] Ran Wei,[l] Astra M. Liepa,[m] Roberto Carlesi,[m] Michael Emig,[m] Atsushi Ohtsu[n]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Association of Best Percent Change in Tumor Size with Best Improvement in Selected Symptoms



Cascinu S et al. *Oncologist* 2021;26(3):e414-24.

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Consider how you felt when you got up this morning (eg, energy level, acute or chronic health issues) and compare that to how you generally felt 2 months ago on scale of 1 to 10, with 1 being much worse today and 10 being much better today.

1. 1 – much worse
2. 2
3. 3
4. 4
5. 5 – status quo
6. 6
7. 7
8. 8
9. 9
10. 10 – much better

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PARP Inhibitors in Prostate Cancer
Top Ten List

1. Genomic workup: Metastatic disease?
2. Role of liquid biopsy?
3. BRCA 1 vs BRCA 2? Other germline mutations?
4. Somatic mutations?
5. LOH, HRD scores?
6. Use of platinum agents
7. PARP inhibitors: First-line therapy for mCRPC (PROPEL, MAGNITUDE)
8. PARP inhibitors: Second-line and beyond
9. Prevention and management of toxicity/side effects
10. Resistance mechanisms; PARP inhibitor rechallange

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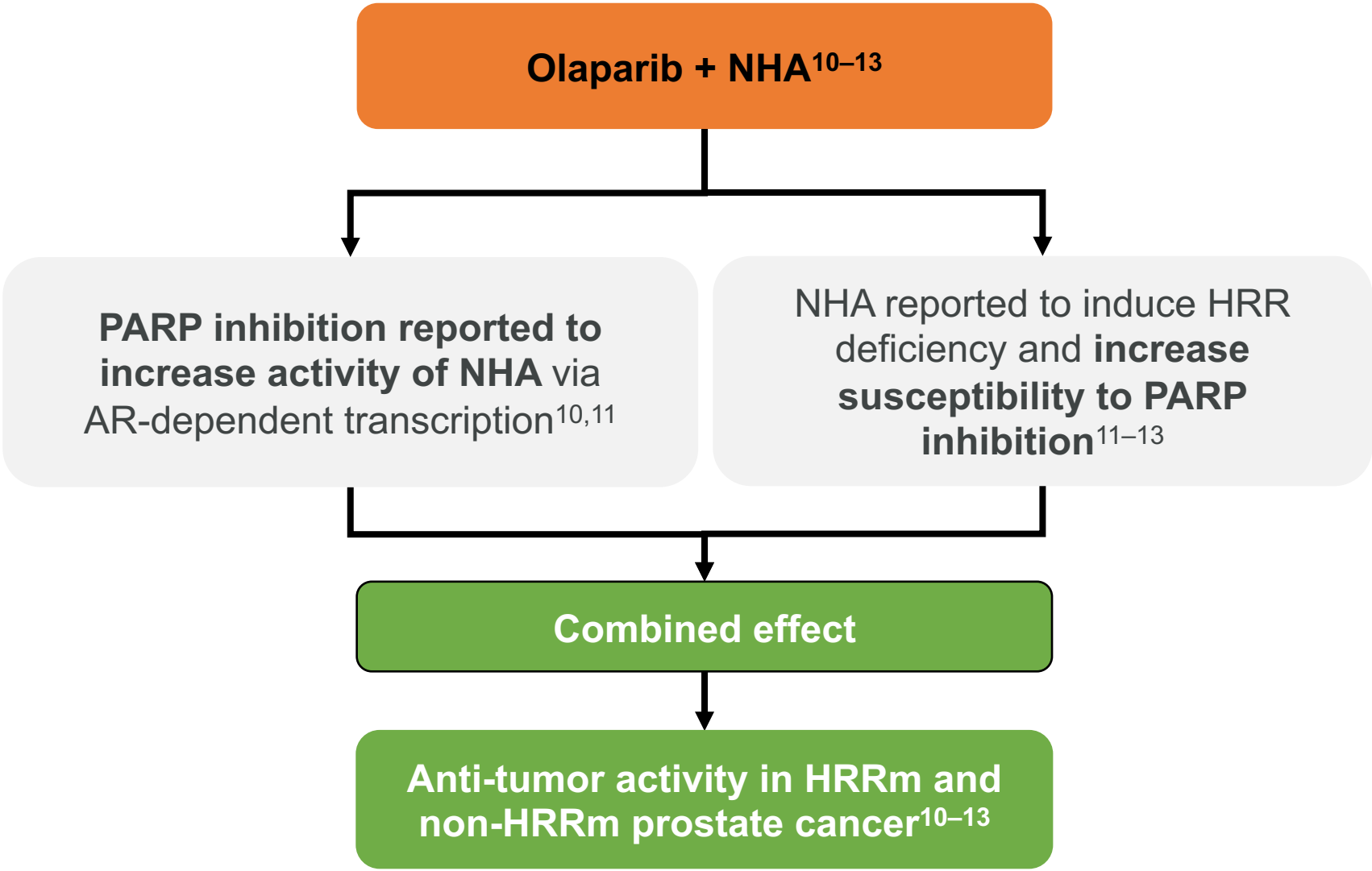
Last but not least in light of the PROpel and MAGNITUDE trials: Is there any rationale for PARPi to work in Pca without DDR?

My opinion:

- Does PARPi block AR signaling?
  - If it did PSA falls would have been seen in non-DDR Pca pts.
- Does AR blockade downregulate HRD and sensitize to PARPi?
  - If it did Abi/enza would hugely increase PARPi RR
- Is there some other MOA?
  - **Possibly;** suggestions of an impact on immune response? STING?
  - Clearance of emerging neuroendocrine clones (RB1/RNASEH2B/BRCA2 lost)
  - Off target effects?

Courtesy of Johann S de Bono, MB ChB, MSc, PhD, FMedSci

Rationale for combining PARP inhibitors and NHAs



1. Mateo J, et al. *N Engl J Med* 2015;373:1697–1708; 2. Schiewer MJ, et al *Cancer Discov* 2012;2:1134–1149; 3. Polkinghorn WR, et al. *Cancer Discov* 2013;3:1245–1153; 4. Asim M, et al. *Nat Commun* 2017;8:374

Courtesy of Fred Saad, MD

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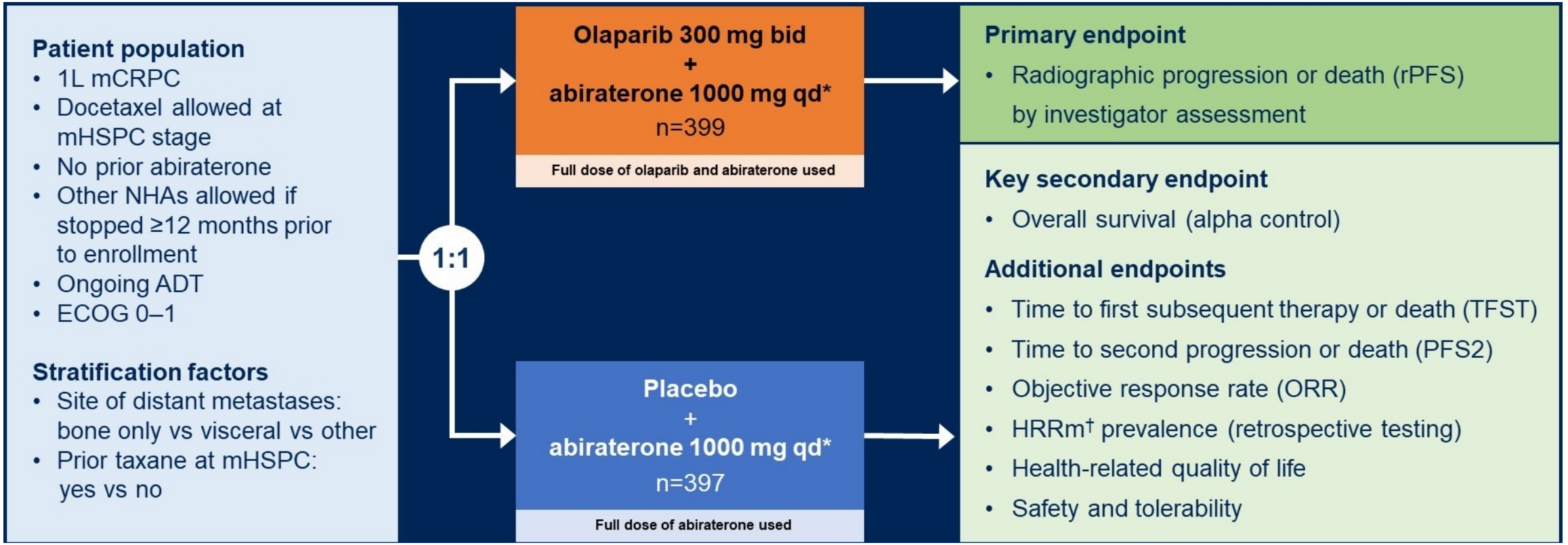
PROpel

Randomized, double-blind, placebo-controlled Phase III trial



Baseline demographics:
HRRm status

HRRm status†		
HRRm	111 (27.8)	115 (29.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)

Courtesy of Fred Saad, MD

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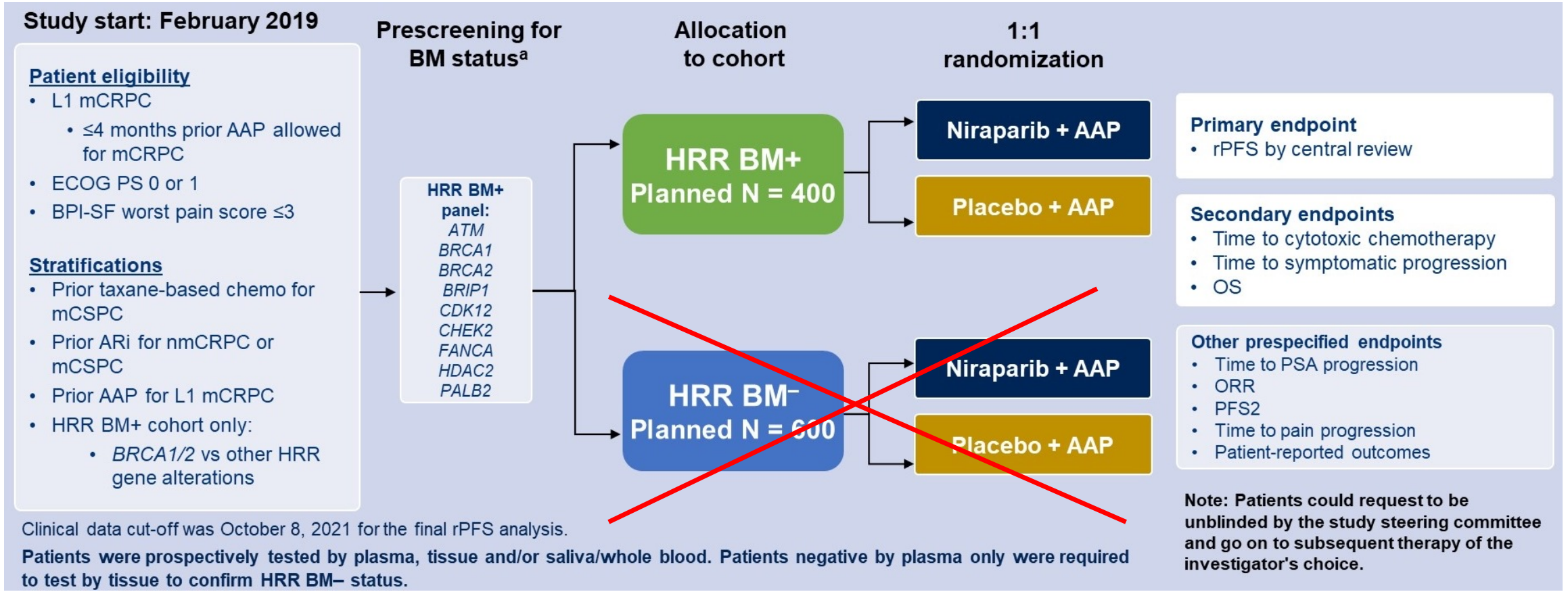
MAGNITUDE

Randomized, double-blind, placebo-controlled Phase III trial



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in partnership with
The ROYAL MARSDEN
NHS Foundation Trust

PARP inhibition for Prostate Cancer

Johann Sebastian de Bono

Regius Professor, Head of the Drug Development Unit,
The Institute of Cancer Research and Royal Marsden Hospital,
London, United Kingdom

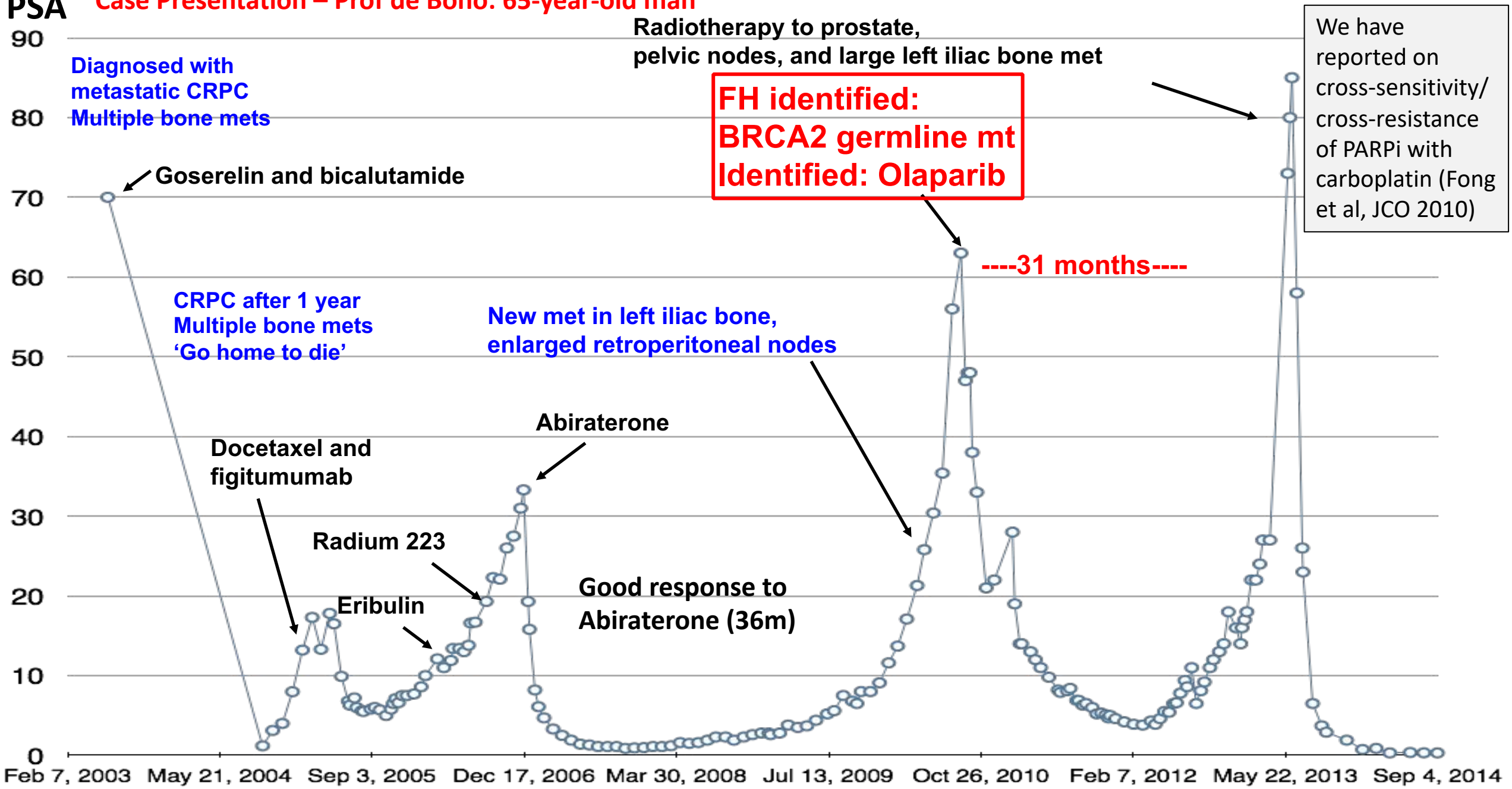
June 2022

Conclusions

- Synthetic lethality strategies can change prostate cancer care
  - PARP inhibitors and platinum cross-resistant
- Germline DDR testing now a standard of care
  - And family cascade testing
  - Please remember to take a family history
- Increasingly complex predictive biomarkers
  - **Biallelic loss necessary to sensitize** to PARPi/platinum
  - BRCA2 homozygous deletions result in longer responses than BRCA2 mutations
  - ATM loss does sensitize to PARPi
  - MMRd and PD-1/PD-L1 targeting ICI
- Beware risks of plasma ctDNA NGS
  - Median tumour fraction 10-30% (ie 70-90% of DNA not tumor DNA)
  - Can miss (BRCA2) HOMDELs (super responders)
  - Can also mistake clonal hemopoietic (CHIP) mutations for tumor mutations

Courtesy of Johann S de Bono, MB ChB, MSc, PhD, FMedSci

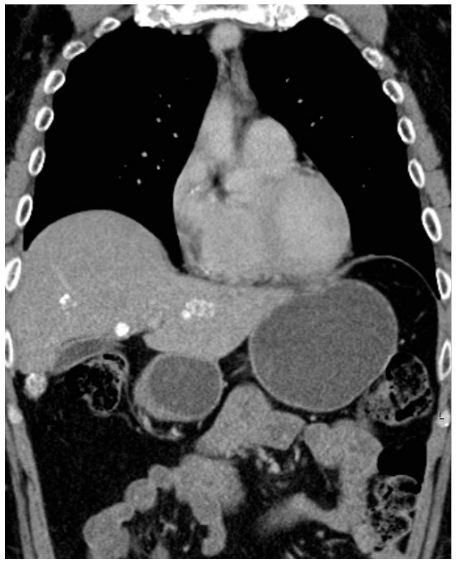
Case Presentation – Prof de Bono: 65-year-old man

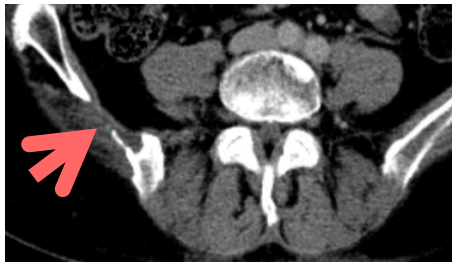


Courtesy of Johann S de Bono, MB ChB, MSc, PhD, FMedSci

Case Presentation – Prof de Bono
HRD and carboplatin response

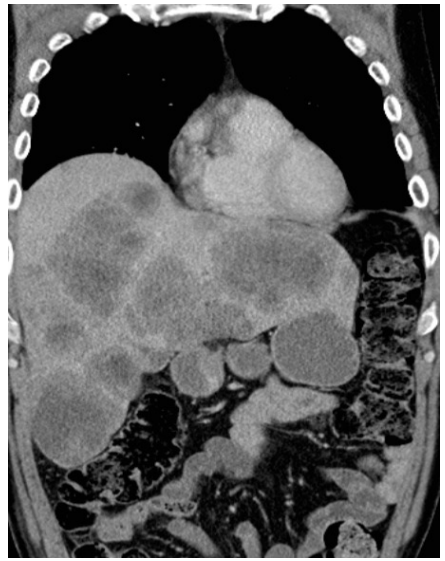
Almost complete resolution of liver metastases with residuum calcified abnormality

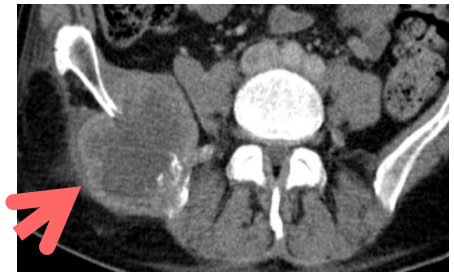




Healing lytic
Bone metastasis

Treatment?





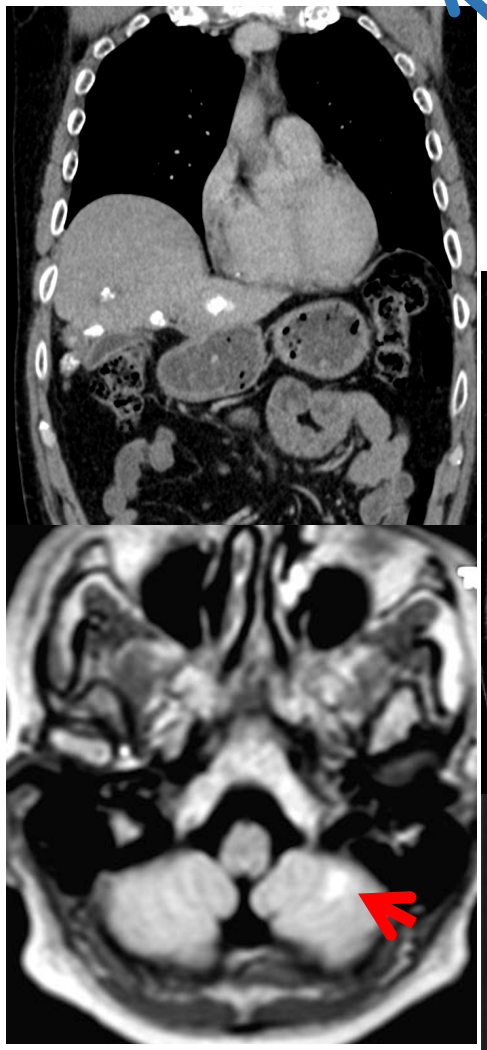
March 2015

Dying man.
Age 44
Strong FH.
LFTs↑
Referred post-abi, enza, docetaxel, cabazitaxel

Courtesy of Johann S de Bono, MB ChB, MSc, PhD, FMedSci

Courtesy of Johann S de Bono, MB ChB, MSc, PhD, FMedSci

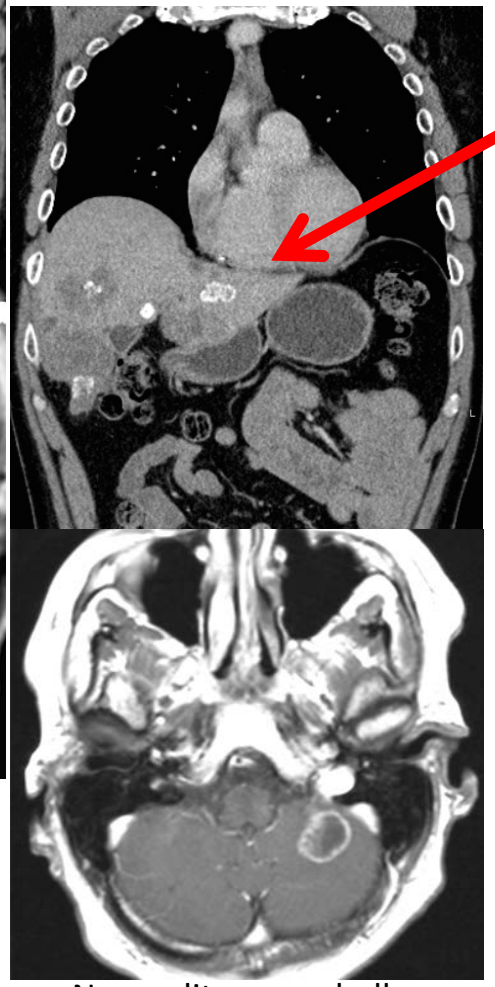
February 2017



Cyberknife planning MRI

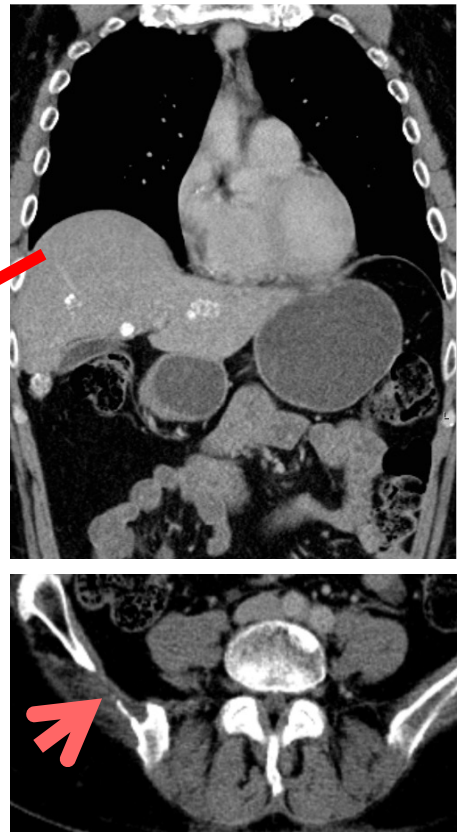
Retreated with carbo AUC6

Relapse after **8 months**



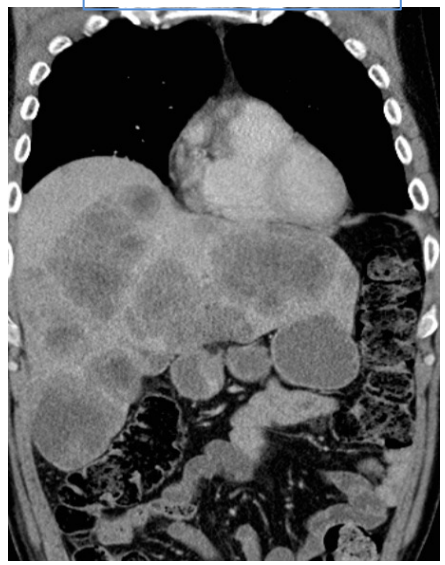
New solitary cerebellar metastasis

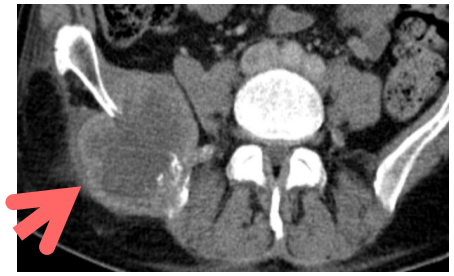
Almost complete resolution of liver metastases with residuum calcified abnormality



Healing lytic Bone metastasis

Carboplatin AUc6 q21d





March 2015

Dying man.
M1 at diagnosis
Strong FH.
Referred post-abi, enza, docetaxel, cabazitaxel.
LFTs↑

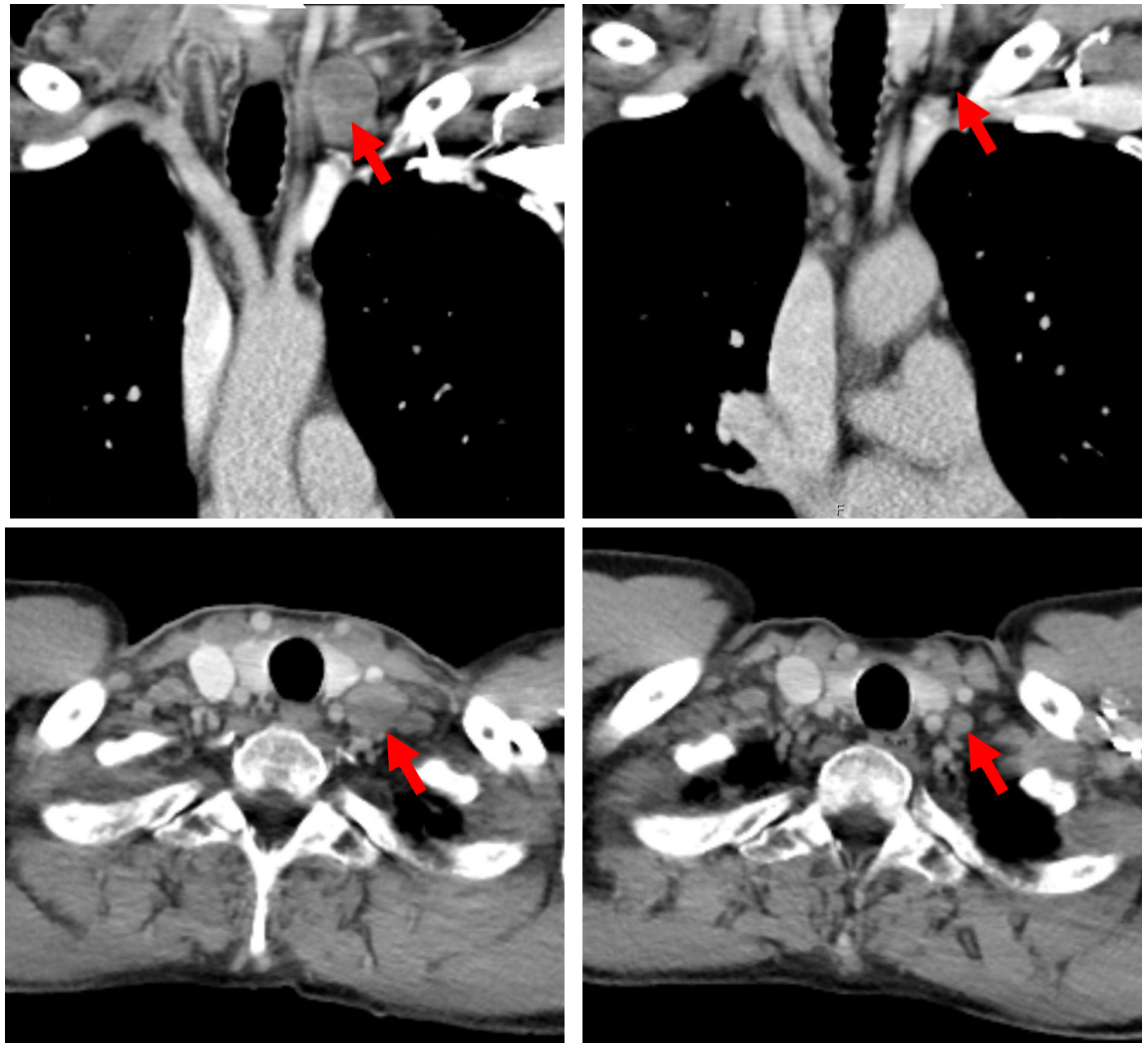
4-year long remission!

Very high HRD score on exome NGS

PALB2 altered mCRPC responding patient on TOPARP-B

Baseline

Best response



29.05.18

29.07.19

Coronal and Axial Contrast Enhanced CT images at baseline and during treatment: Complete response (PR) of left supraclavicular lymphadenopathy (arrows). Patient also had very good response at the sites of small volume lymphadenopathy. This response lasted > 1 year in late stage mCRPC.

Patient had bi-allelic PALB2 loss.

Courtesy of Johann S de Bono, MB ChB, MSc, PhD, FMedSci

Agenda

Introduction: This Week on RTP

MODULE 1: PARP Inhibitors in Prostate Cancer – Top 10 List

MODULE 2: Optimal Integration of PARP Inhibitor Monotherapy into the Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC) – Prof de Bono

MODULE 3: Available Data with, Ongoing Investigation of and Potential Future Role for PARP Inhibitor-Based Combination Strategies – Dr Saad

RTP
RESEARCH
TO PRACTICE

Opening the door for PARPi treatment: What lies ahead?

Fred Saad MD FRCS

Professor and Chairman of Urology

Director of GU Oncology

Raymond Garneau Chair in Prostate Cancer

University of Montreal Hospital Center

Montreal, QC, Canada

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Conclusion

- Survival of men with mCRPC in the real world remains a problem
- Good first line options but early resistance/progression is a challenge
- Second line options are available **but** many patients do not get more than 1 line of effective therapy in the real world
- Less than half the men with prostate cancer will receive chemotherapy before dying from prostate cancer
- Building on effective first line options for mCRPC is critically needed
- PARP/NHT combination fulfills an unmet need of effective and tolerable first line combinations
  - In all patients? Only in HRR mutated?

Courtesy of Fred Saad, MD

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Successful phase 3 trials in mCRPC

Study	Agents	N	Indication	HR	ΔOS (mo)
TAX-327[1]	DOC / P vs mito / P	1006	mCRPC, symptomatic or not	0.76	+2.9
COU-AA-302[2]	ABI / P vs P	1088	mCRPC (pre-DOC), mild / no symptoms No visceral metastases	0.81	+4.4
COU-AA-301[3]	ABI / P vs P	1195	mCRPC (post-DOC)	0.74	+4.6
PREVAIL[4]	ENZ vs PBO	1717	mCRPC (pre-DOC), mild / no symptoms	0.77	+4.0
AFFIRM[5]	ENZ vs PBO (or P)	1199	mCRPC (post-DOC)	0.63	+4.8
TROPIC[6]	CABA / P vs mito / P	755	mCRPC (post-DOC)	0.70	+2.4
ALSYMPCA[7]	Radium-223 vs PBO	921	mCRPC (post-DOC or unfit for DOC)	0.70	+3.6
PROfound[8]	Olaparib vs NHT	245	mCRPC post-NHT (with HRRm)	0.69	+4.4
VISION[9]	Lu-PSMA vs NHT	831	mCRPC post-NHT (with PSMA+) and chemo	0.62	+4.0

All studies had a non life-prolonging control arm

Courtesy of Fred Saad, MD

ABI, abiraterone; CABA, cabazitaxel; chemo, chemotherapy; DOC, docetaxel; ENZ, enzalutamide; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; Lu-PSMA, Lutetium-177 prostate-specific membrane antigen; mCRPC, metastatic castration-resistant prostate cancer; mito, mitoxantrone; mo, months; NHT, neoadjuvant hormonal therapy; OS, overall survival; P, prednisone; PBO, placebo

1. Tannock IF, et al. *N Engl J Med* 2004;351:1502–1512; 2. Ryan CJ, et al. *Lancet Oncol* 2015;16:152–160; 3. Rathkopf DE, et al. *Eur Urol* 2014;66:815–825; 4. Beer TM, et al. *Eur Urol* 2017;71:151–154; 5. Armstrong AJ, et al. *Cancer* 2017;123:2303–2311; 6. de Bono JS, et al. *Lancet* 2010;376:1147–1154; 7. Hoskin P, et al. *Lancet Oncol* 2014;15:1397–1406; 8. Hussain M, et al. *N Engl J Med* 2020;383:2345–2357; 9. Sartor O, et al. Online ahead of print. *N Engl J Med* 2021

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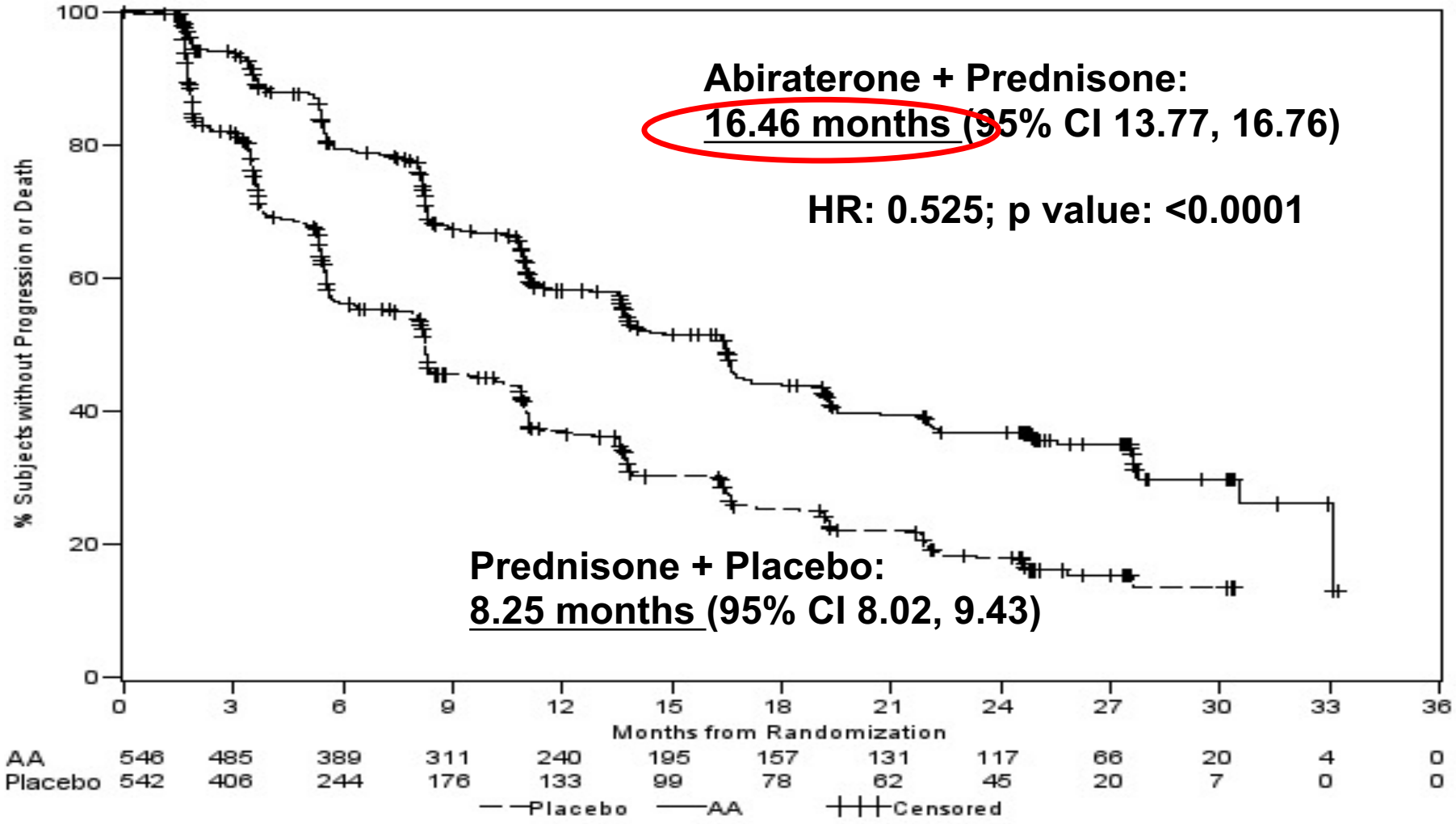
Standard of care Abiraterone: rPFS



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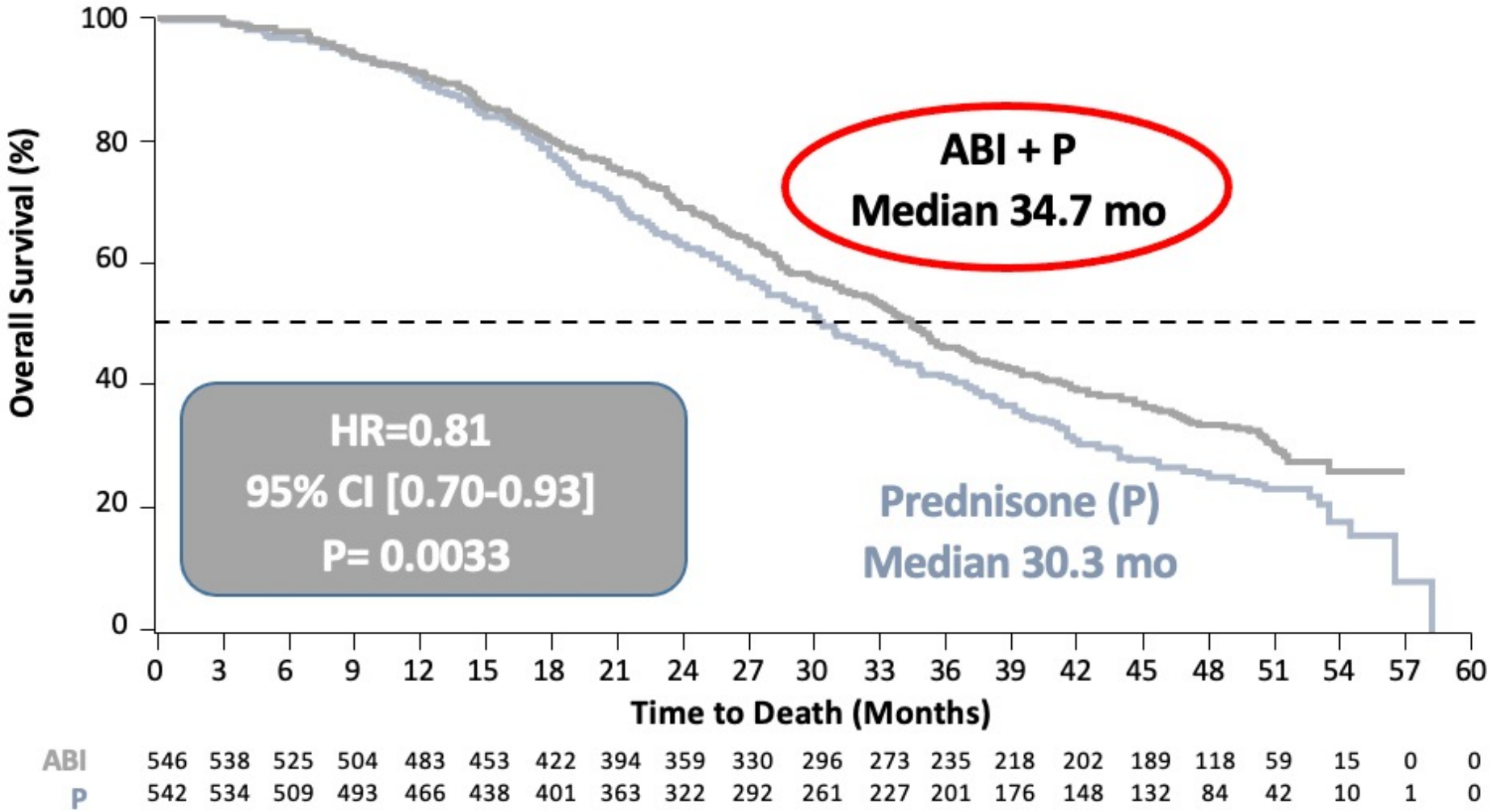
Abiraterone First Line – Overall Survival



Ryan CJ et al. *Lancet Oncol*. 2015;16: 152-60

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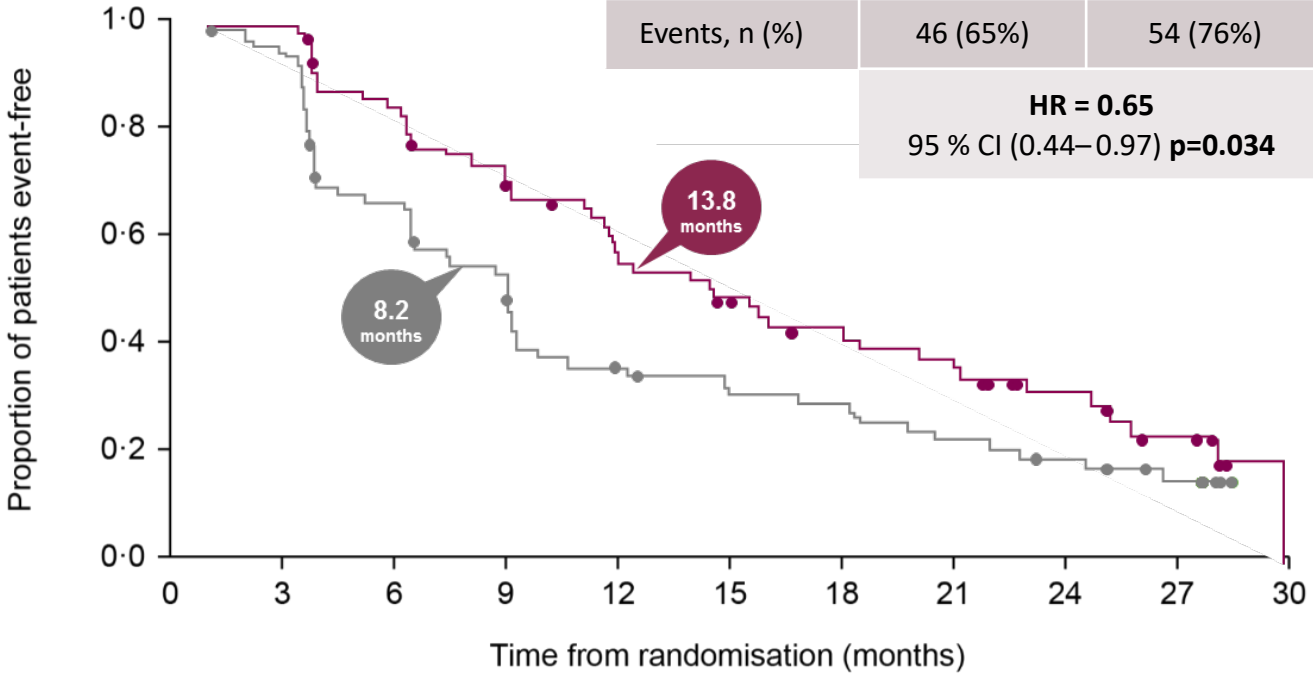
Phase 2 study

Olaparib + abiraterone significantly prolonged rPFS vs. placebo + abiraterone in patients irrespective of HRRm status[1,2]

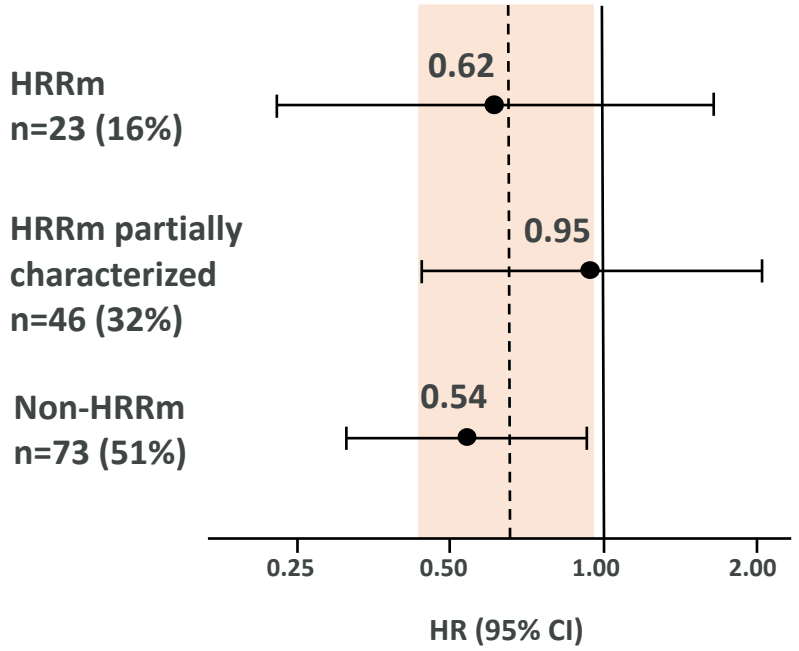
A 35% decrease in the risk of disease progression or death was seen in the olaparib + abiraterone arm[1]

Investigator-assessed rPFS[1]

	Olaparib + abiraterone (n=71)	Placebo + abiraterone (n=71)
Events, n (%)	46 (65%)	54 (76%)
	HR = 0.65 95 % CI (0.44–0.97) **p=0.034**	



rPFS by HRRm subgroup[2*]



*Dashed line and shaded area show HR and 95% CI, respectively, for the intent to treat population

CI=confidence interval; HR=hazard ratio; HR=hazard ratio; HRRm=homologous recombination repair gene mutation; rPFS=radiographic progression free survival

1. Clarke N. et al. *Lancet Oncol* 2018;19(7):975–986; 2. Carr TH, et al. *Cancers* 2021;13(22):5830.

Courtesy of Fred Saad, MD

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NEJM Evidence

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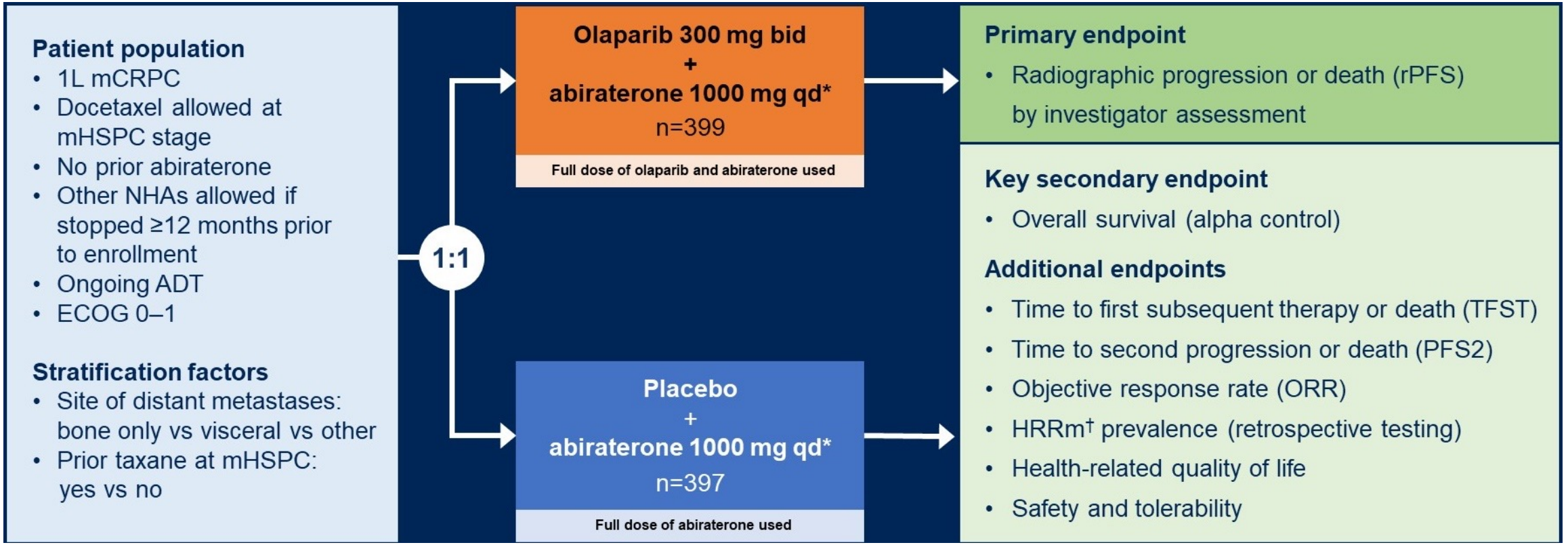
ORIGINAL ARTICLE

Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer

Noel W. Clarke, M.B.B.S., Ch.M., F.R.C.S.,[1] Andrew J. Armstrong, Sc.M., M.D.,[2] Antoine Thiery-Vuillemin, M.D., Ph.D.,[3] Mototsugu Oya, M.D.,[4] Neal Shore, M.D.,[5] Eugenia Loredo, M.D.,[6] Giuseppe Procopio, M.D.,[7] Juliana de Menezes, M.D.,[8] Gustavo Girotto, M.D.,[9] Cagatay Arslan, M.D.,[10] Niven Mehra, M.D., Ph.D.,[11] Francis Parnis, F.R.A.C.P.,[12] Emma Brown, M.D.,[13] Friederike Schlürmann, M.D.,[14] Jae Y. Joung, M.D., Ph.D.,[15] Mikio Sugimoto, M.D., Ph.D.,[16] Juan A. Virizuela, M.D., Ph.D.,[17] Urban Emmenegger, M.D.,[18] Jiri Navratil, M.D.,[19] Gary L. Buchschacher, Jr., M.D., Ph.D.,[20] Christian Poehlein, M.D.,[21] Elizabeth A. Harrington, Ph.D.,[22] Chintu Desai, Ph.D.,[23] Jinyu Kang, M.D.,[24] Fred Saad, M.D., F.R.C.S.,[25] for the PROpel Investigators*

PROpel

Randomized, double-blind, placebo-controlled Phase III trial



Baseline demographics:
HRRm status

HRRm status†		
HRRm	111 (27.8)	115 (29.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)

Courtesy of Fred Saad, MD

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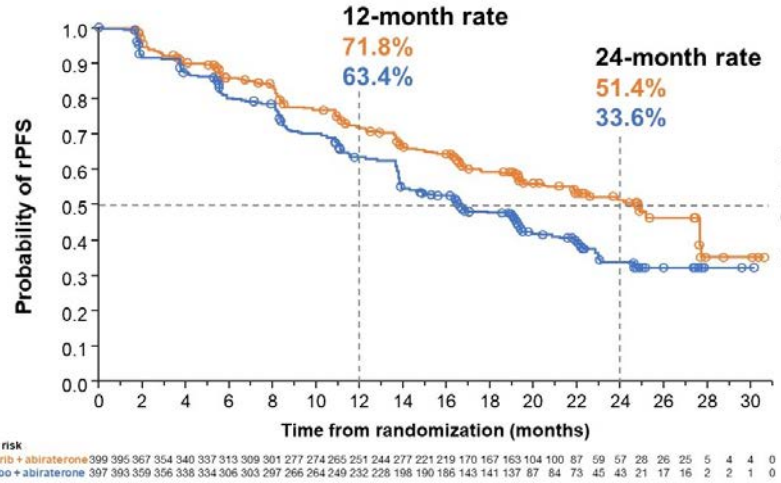
PROpel

Primary endpoint

rPFS by investigator assessment

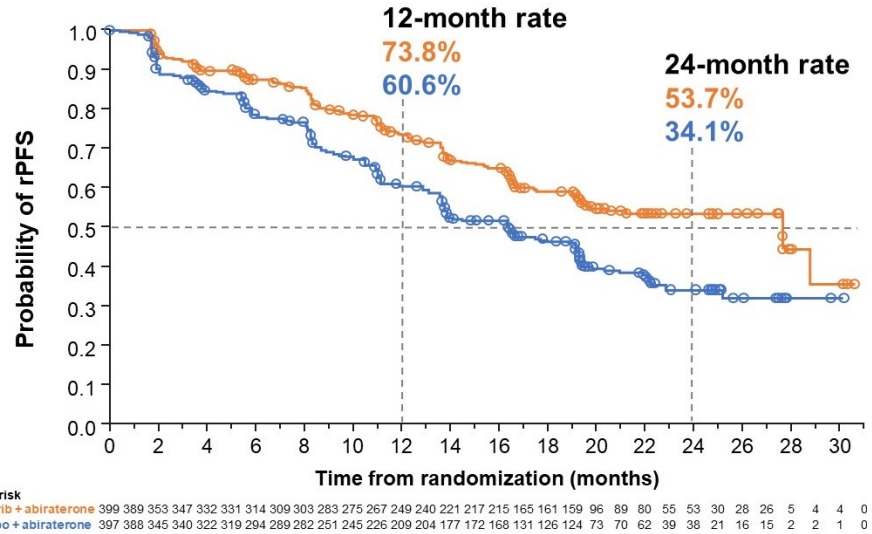


	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

rPFS by blinded independent central review^



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001†	

Median rPFS improvement of 11.2 months favors olaparib + abiraterone‡

- **34% risk reduction for progression or death with olaparib + abiraterone (HR 0.66; 95% CI 0.54–0.81; *P*<0.0001)**

Saad F, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #11

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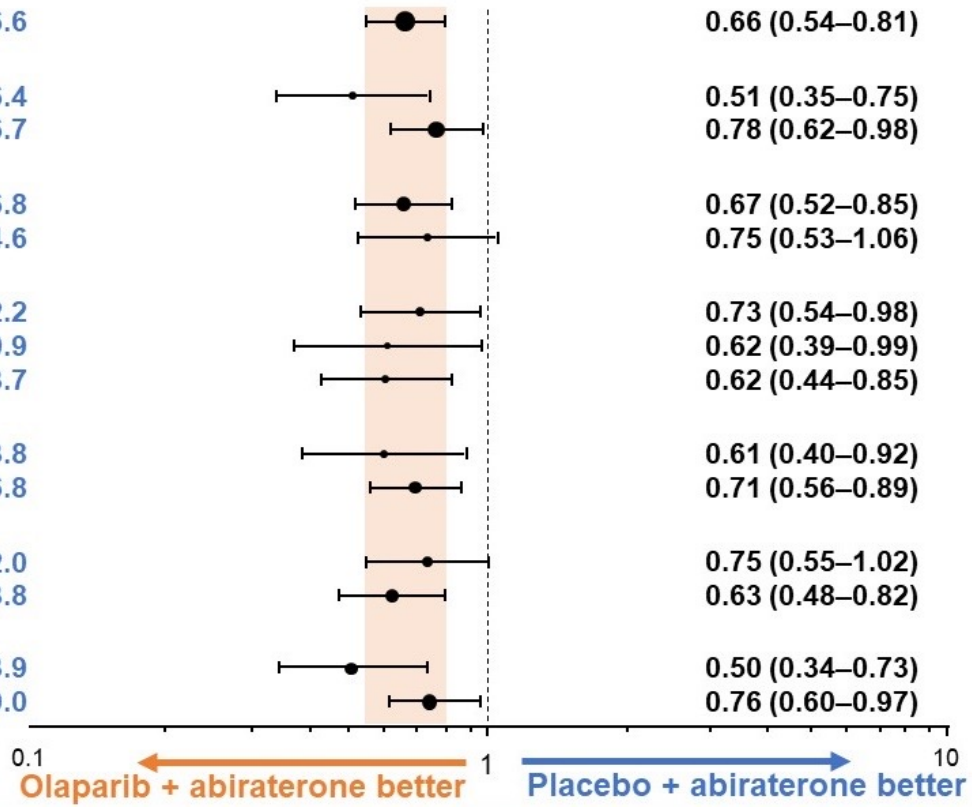
rPFS subgroup analysis

	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	0.66 (0.54–0.81)
Age at randomization				
<65	227	NR	16.4	0.51 (0.35–0.75)
≥65	569	22.0	16.7	0.78 (0.62–0.98)
ECOG performance status at baseline				
0	558	24.9	16.8	0.67 (0.52–0.85)
1	236	17.5	14.6	0.75 (0.53–1.06)
Site of distant metastases				
Bone only	434	27.6	22.2	0.73 (0.54–0.98)
Visceral	105	13.7	10.9	0.62 (0.39–0.99)
Other	257	20.5	13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	0.61 (0.40–0.92)
No	607	24.8	16.8	0.71 (0.56–0.89)
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	0.75 (0.55–1.02)
Above or equal to median baseline PSA	397	18.5	13.8	0.63 (0.48–0.82)
HRRm status*				
HRRm	226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	552	24.1	19.0	0.76 (0.60–0.97)



- **rPFS benefit observed across all pre-specified subgroups**

Saad F, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #11

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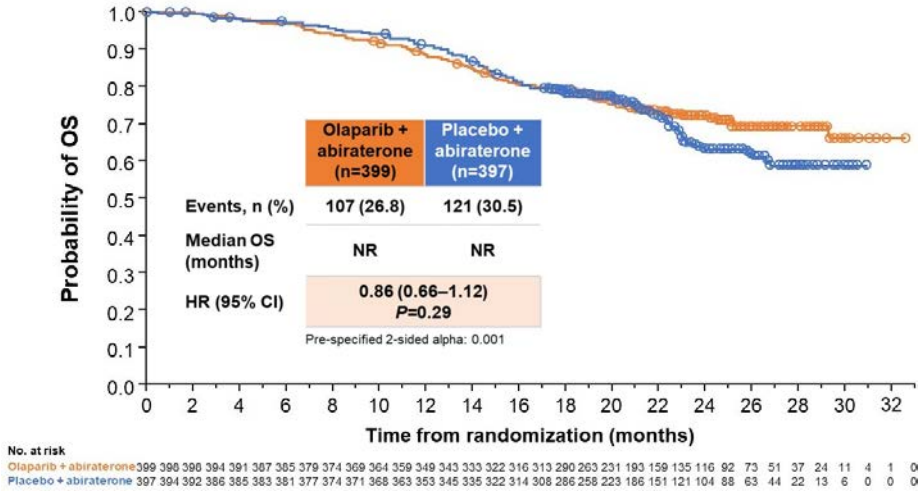
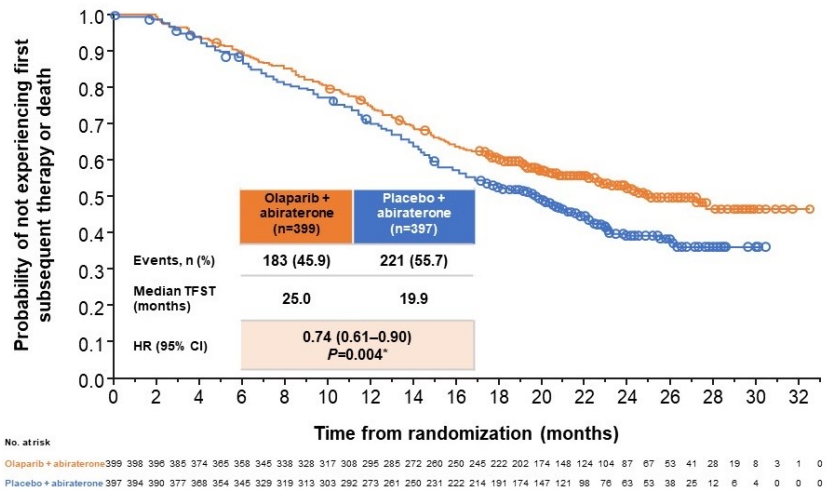
Key secondary endpoints

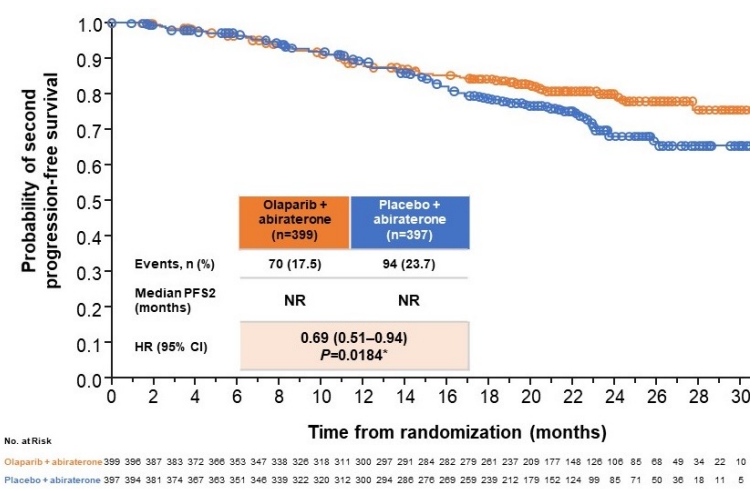
Overall survival



Time to first subsequent therapy or death (TFST)



Time to second progression or death (PFS2)



- OS data immature, but trend towards improved OS with olaparib + abiraterone
- TFST (HR 0.74; 95% CI 0.61–0.90) and PFS2 (HR 0.69; 95% CI 0.51–0.94) supportive of long-term benefits

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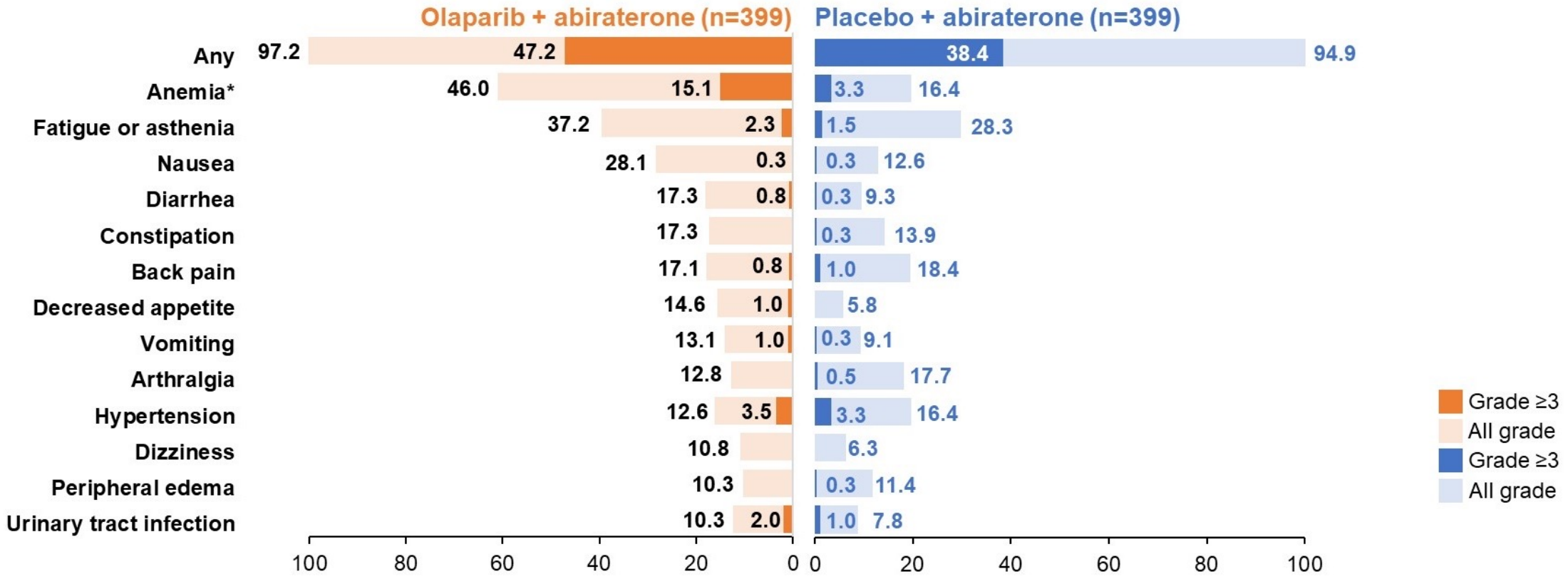
Safety data



- Safety and tolerability profile consistent with the known safety profiles of individual drugs
- The most common grade ≥3 AE was anemia (15.1% vs 3.3%)

*Anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events v4.03.
Saad F, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #11

Courtesy of Fred Saad, MD

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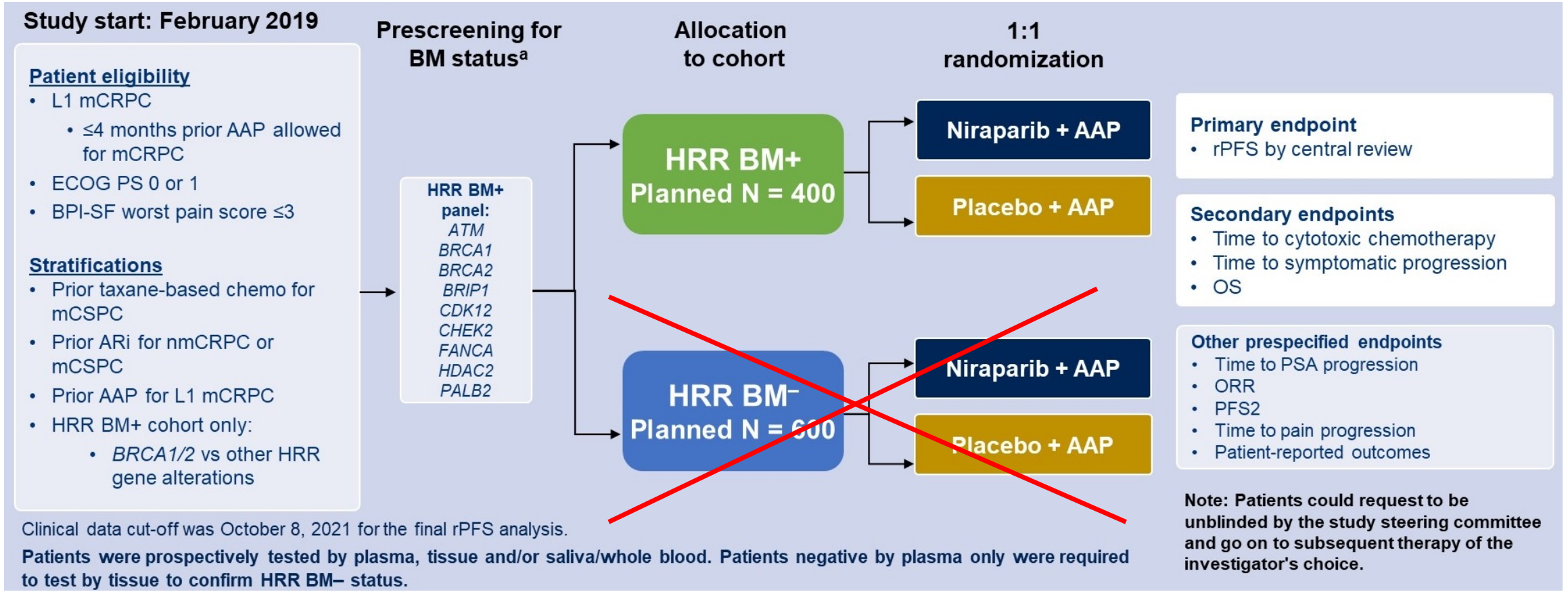
MAGNITUDE

Randomized, double-blind, placebo-controlled Phase III trial



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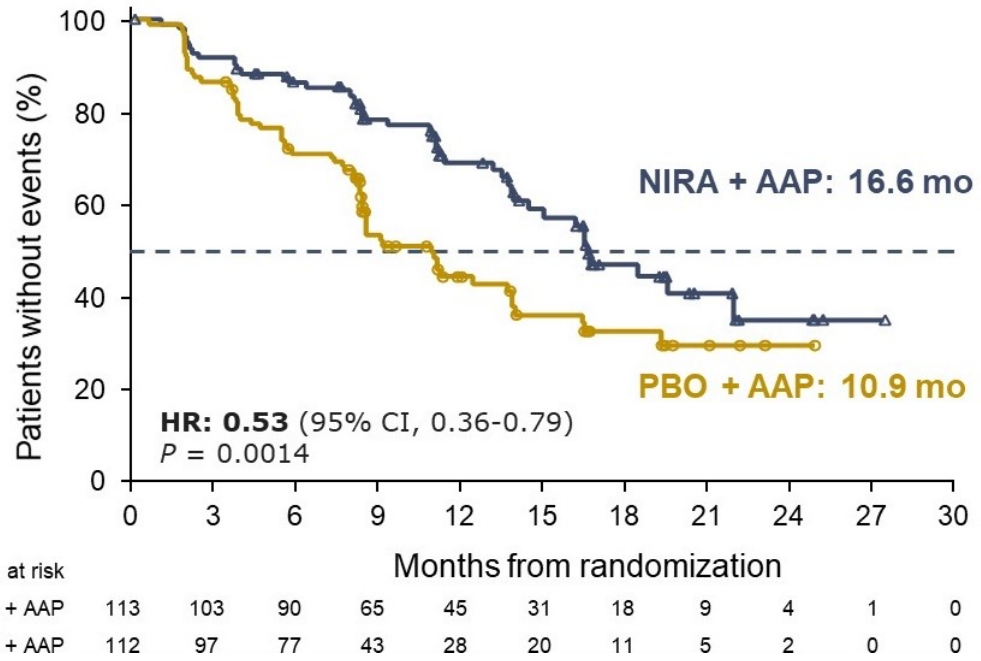
MAGNITUDE

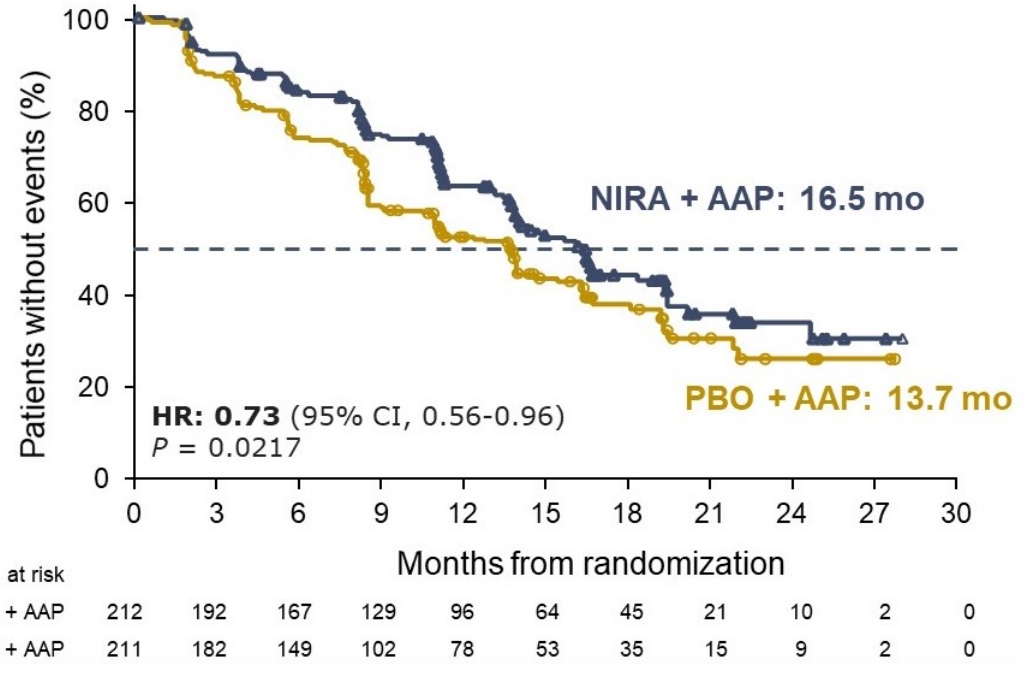
Primary endpoint: rPFS by central review

BRCA1/2-mutated



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

All HRR BM+



No. at risk											
NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

- 47% improvement in rPFS in patients with *BRCA1/2* alterations (HR 0.53; 95% CI 0.36–0.79; *P*=0.0014)
- 27% improvement in rPFS across all HRR BM+ patients (HR 0.73; 95% CI 0.56–0.96; *P*=0.0217)

Chi KN, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #12

Courtesy of Fred Saad, MD

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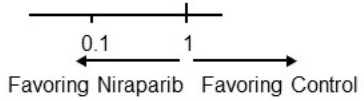
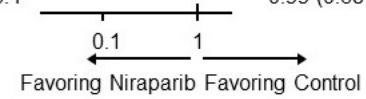
MAGNITUDE

rPFS subgroup analysis: All HRR BM+

Variable	Subgroup	Median (months) niraparib	Median (months) control	HR (95% CI)	Events/N niraparib	Events/N control
All HRR+ patients	All	16.5	13.7	0.74 (0.57–0.97)	100/212	117/211
Age group	<65	13.9	13.9	1.01 (0.61–1.66)	32/61	30/62
	≥65-74	19.4	13.6	0.58 (0.38–0.89)	34/88	57/100
	≥75	16.4	10.9	0.76 (0.46–1.24)	34/63	30/49
Race group	Asian	22.0	10.9	0.48 (0.22–1.05)	9/29	22/41
	White	14.4	13.8	0.83 (0.61–1.13)	82/160	83/153
	Other	18.4	9.0	0.47 (0.20–1.14)	9/23	12/17
Baseline ECOG performance status	0	19.5	13.9	0.65 (0.46–0.92)	53/130	76/146
	1	13.1	10.5	0.84 (0.55–1.28)	47/82	41/65
Baseline BPI-SF#3 Score	0	16.7	16.8	0.75 (0.51–1.12)	47/108	53/103
	1 to 3	13.9	10.5	0.78 (0.52–1.17)	46/88	50/86
	>3	13.7	13.7	0.68 (0.26–1.79)	6/14	14/22
Region	Asia Pacific	19.5	13.8	0.64 (0.35–1.17)	17/43	27/52
	Europe	14.4	13.7	0.82 (0.58–1.14)	68/128	71/120
	North and South America	16.6	16.4	0.60 (0.30–1.18)	15/41	19/39
Past taxane–based chemotherapy	Yes	13.4	10.9	0.89 (0.48–1.66)	20/40	21/41
	No	16.6	13.8	0.71 (0.53–0.96)	80/172	96/170
Past androgen receptor-targeted therapy[a]	Yes	NE	4.3	0.19 (0.03–1.23)	2/8	3/4
	No	16.5	13.8	0.76 (0.58-1.00)	98/204	114/207
Prior AAP use[b]	Yes	13.9	14.6	0.95 (0.54–1.67)	23/47	26/45
	No	16.7	12.7	0.71 (0.52–0.96)	77/165	91/166
Presence of visceral metastases	Yes	11.0	8.1	1.03 (0.60–1.77)	34/51	22/39
	No	19.4	13.8	0.64 (0.47–0.87)	66/161	95/172
Bone only metastasis at entry	Yes	19.4	15.4	0.72 (0.45–1.14)	32/78	41/85
	No	14.8	10.9	0.73 (0.53–1.02)	68/134	76/126
Number of bone lesions at baseline	≤10	19.4	15.4	0.76 (0.53–1.10)	54/127	65/128
	>10	13.8	8.4	0.69 (0.47–1.04)	46/85	52/83
Baseline PSA above median	Yes	15.7	8.3	0.58 (0.40–0.82)	56/110	66/101
	No	16.7	18.2	0.93 (0.62–1.40)	44/102	51/110
Gene mutation type	BRCA	16.6	10.9	0.55 (0.38–0.81)	45/113	64/112
	Other HRR	14.8	16.4	0.99 (0.68–1.45)	55/99	53/99





Chi KN, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #12

Courtesy of Fred Saad, MD

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MAGNITUDE

Safety data: HRR BM+

Treatment-emergent adverse events occurring at >20% in the NIRA arm or otherwise of clinical interest, n (%)		NIRA + AAP, n = 212		PBO + AAP, n = 211	
		All grades	Grade ≥3	All grades	Grade ≥3
Hematologic	Anemia	98 (46.2)	63 (29.7)	43 (20.4)	16 (7.6)
	Thrombocytopenia	45 (21.2)	14 (6.6)	18 (8.5)	5 (2.4)
	Neutropenia	29 (13.7)	14 (6.6)	12 (5.7)	3 (1.4)
	Acute myeloid leukemia/ Myelodysplastic syndrome	0	0	1 (0.5)	1 (0.5)
Cardiovascular	Hypertension	67 (31.6)	33 (15.6)	47 (22.3)	30 (14.2)
	Arrhythmia	27 (12.7)	6 (2.8)[a]	12 (5.7)	3 (1.4)
	Cardiac failure	4 (1.9)	3 (1.4)[a]	4 (1.9)	1 (0.5)
	Ischemic heart disease	4 (1.9)	4 (1.9)	8 (3.8)	6 (2.8)[b]
General disorders	Fatigue	56 (26.4)	7 (3.3)	35 (16.6)	9 (4.3)
Gastrointestinal	Constipation	65 (30.7)	–	29 (13.7)	–
	Nausea	50 (23.6)	1 (0.5)	29 (13.7)	0
Hepatotoxicity		25 (11.8)	4 (1.9)	26 (12.3)	10 (4.7)
Cerebrovascular disorders		6 (2.8)	2 (0.9)	2 (0.9)	1 (0.5)[a]

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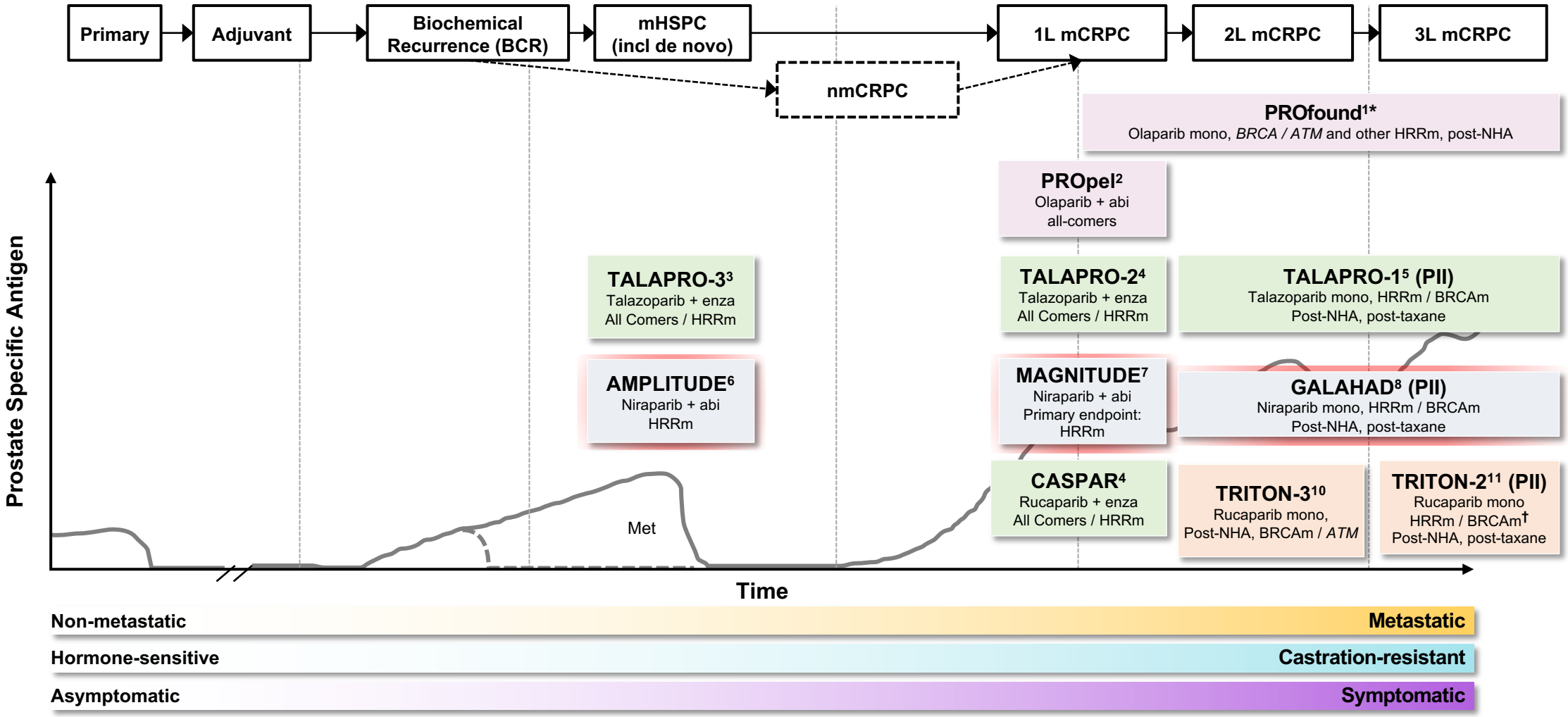
Ongoing trials investigating PARPi in advanced PC



Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 61-year-old patient

- Presented with moderate LUTS
- No relevant past medical history
- PSA 132 with suspicious T3 disease on DRE
- Biopsy reveals 9/12 cores with Gleason 4 + 4 adenocarcinoma
- Bone scan:
  - Multiple metastases in the hip, lumbar spine, and 8th left rib
- Abdominal/thoracic CT scan:
  - Suspicious retroperitoneal lymph nodes between and lung metastases

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 61-year-old patient (continued)

- Patient received ADT + 6 cycles of docetaxel
- PSA nadir of 0.9 after 12 months
- 6 months later: PSA rises to 1.6
- 6 months later: PSA 3.4
- Slight discomfort lumber spine
- Imaging reveals progression of lymph nodes, stable otherwise

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 61-year-old patient (continued)

- Began PROpel study of abiraterone +/- olaparib in February 2019
- Well tolerated except for slight fatigue and decline in hemoglobin from 13.3 to 10.5 after 3 months
- Rise in Hb after 8 months to 12.5 and remains stable
- PSA < 0.02 after 6 months
- Imaging: CR of all measurable lesions and no change on bone scan
- Continues to be seen monthly and remains in complete response

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 75-year-old patient

- History of well controlled hypertension
- Known family history of breast and ovarian cancer
- Patient known to be germline BRCA2 carrier
- Patient found to have metastatic prostate cancer at diagnosis
- Became mCRPC 2 years after start of ADT
- Started on enzalutamide 4 years ago
- PSA declines from 16 to 6

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 75-year-old patient (continued)

- PSA rises to 10 and radiographic progression 15 months later
  - Bone scan: metastases hip and lumbar spine
  - Abdominal/thoracic CT scan: multiple retroperitoneal lymph nodes up to 3 cm
- Patient started on olaparib
  - Well tolerated with minor fatigue
  - PSA declines to 0.2
  - Imaging: lymph nodes all below 1 cm, reduced intensity on bone scan
- Patient remained without progression for 18 months

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 75-year-old patient (continued)

- PSA began to rise and progression of metastases on imaging with eventual progression of pain
- Patient went on to receive docetaxel
- Some relief of pain and PSA reduction after 4 cycles
- Progression of PSA, imaging and symptoms after 8 cycles
- Patient allowed early access to ^{177}Lu-PSMA-617
- Presently stable after 2 cycles and tolerating well

Courtesy of Fred Saad, MD

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Consider how prepared you feel right now to administer a PARP inhibitor to a patient with mCRPC compared to how prepared you felt before this webinar. How would you rate your current preparedness on a scale of 1 to 10, with 1 being much less prepared now and 10 being much more prepared now?

1. 1 – much less prepared
2. 2
3. 3
4. 4
5. 5 – status quo
6. 6
7. 7
8. 8
9. 9
10. 10 – much more prepared

RTP
RESEARCH TO PRACTICE

Backup Slides

Case Presentation – Dr Saad: 74-year-old patient

- Long history of prostate cancer
- Diagnosed with metastatic disease 5 years prior to referral
- Received ADT at diagnosis, then received treatment for mCRPC
  - Abiraterone
  - Docetaxel
  - Cabazitaxel
- Referred in desperation for clinical trial
  - ECOG PS 2 with chest tubes for pleural effusion
  - Multiple bone, lymph node and lung metastases
  - PSA 4,222

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 74-year-old patient (continued)

- Patient eligible for GALAHAD trial IF found to have HRRm
- Patient tested and was positive for BRCA2
- Started open label niraparib monotherapy
- After 1 month patient started to feel better and breathing improved
- After 4 months pleural effusion had stopped and chest tubes could be removed
- PSA declined to 1,230, patient resumed all his previous activities and continued to drive 3 hours every month for his visits
- Remained responsive for 22 months even with PSA rising up to 5,100

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 74-year-old patient (continued)

- Referred for clinical trial following progressive mCRPC
- Had received ADT for de novo metastatic prostate cancer diagnosed 3 years prior
- After rapid progression to mCRPC had received docetaxel followed by enzalutamide
- Rapid progression of disease on enzalutamide

- Patient ECOG PS 0-1 with pain requiring narcotics, otherwise active
- Patient accepted open label phase 1 study of niraparib + abiraterone

Courtesy of Fred Saad, MD

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Case Presentation – Dr Saad: 74-year-old patient (continued)

- Full dose niraparib and abiraterone started on study
- Patient had some relief of pain but developed grade 3 anemia and thrombocytopenia
- Niraparib held, patient transfused
  - Anemia and thrombocytopenia returned to grade 1
- Resumed niraparib at reduced dose of 200 mg BID
- Tolerated drug but again experienced grade 3 thrombocytopenia
- Treatment stopped but disease progressed shortly after
- Patient started on cabazitaxel with little success

Courtesy of Fred Saad, MD

CHUM

Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, June 28, 2022
5:00 PM – 6:00 PM ET

Faculty

Jorge E Cortes, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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