Current Approaches and Future Strategies in Oncology: A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists and Research Institute

A CME/MOC- and NCPD-Accredited Event

Saturday, October 7, 2023
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

CLINICAL SUMMIT 2023

FLORIDA CANCER SPECIALISTS & Research Institute

Welcome FCS Members!

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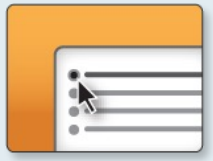
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the premeeting survey.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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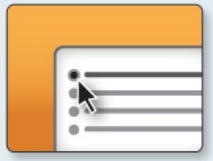
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the premeeting survey at the beginning of each module.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME/NCPD Credit: CME and NCPD credit links will be provided in the chat room at the conclusion of the program. MOC and ONCC credit information will be emailed to attendees within the next 2-3 business days.

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This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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Join Us In Person or Virtually

Oncology in the Real World

A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

Saturday, October 14, 2023

Lymphoma

9:30 AM – 10:30 AM PT
(12:30 PM – 1:30 PM ET)

Faculty

Christopher R Flowers, MD, MS
Ann S LaCasce, MD, MMSc

Urothelial Bladder Cancer and Renal Cell Carcinoma

10:30 AM – 11:30 AM PT
(1:30 PM – 2:30 PM ET)

Faculty

Thomas E Hutson, DO, PharmD
Guru P Sonpavde, MD

Moderator

Neil Love, MD

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Oncology in the Real World

A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

Saturday, October 14, 2023

Hepatobiliary and Pancreatic Cancers

11:50 AM – 12:50 PM PT
(2:50 PM – 3:50 PM ET)

Faculty

Mitesh J Borad, MD
Anthony El-Khoueiry, MD

Gynecologic Cancers

1:30 PM – 2:30 PM PT
(4:30 PM – 5:30 PM ET)

Faculty

Bradley J Monk, MD
Kathleen N Moore, MD, MS

Moderator

Neil Love, MD

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Join Us In Person or Virtually

Oncology in the Real World

A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

Saturday, October 14, 2023

Multiple Myeloma

2:30 PM – 3:30 PM PT
(5:30 PM – 6:30 PM ET)

Faculty

Amrita Krishnan, MD
Robert Z Orlowski, MD, PhD

HER2-Positive and Triple-Negative Breast Cancer

3:50 PM – 4:50 PM PT
(6:50 PM – 7:50 PM ET)

Faculty

Sara A Hurvitz, MD, FACP
Heather McArthur, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

JOIN US IN 2024 FOR THE RETURN OF

The Annual
National General Medical Oncology Summit

A Multitumor CME/MOC- and NCPD-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists and Research Institute

MARCH 22-24, 2024

JW Marriott Miami Turnberry

To Learn More or to Register, Visit
www.ResearchToPractice.com/Meetings/GMO2024

Agenda

Module 1 — ER-Positive Breast Cancer: *Drs Burstein and Jhaveri*

Module 2 — Prostate Cancer: *Drs Morgans and Smith*

Module 3 — Non-Small Cell Lung Cancer: *Drs Riely and Wakelee*

Module 4 — Colorectal and Gastroesophageal Cancers:
Drs Bekaii-Saab and Philip

Module 5 — Chronic Lymphocytic Leukemia: *Drs Chanan-Khan and Kahl*

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Contributing General Medical Oncologists from FCS

Susmitha Apuri, MD
Inverness, Florida

Sunil Gandhi, MD
Lecanto, Florida

Mamta Choksi, MD
New Port Richey, Florida

Shaachi Gupta, MD, MPH
Lake Worth, Florida

Uday Dandamudi, MD
New Port Richey, Florida

Lowell L Hart, MD
Fort Myers, Florida

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Contributing General Medical Oncologists from FCS

Maen Hussein, MD
The Villages, Florida

Vikas Malhotra, MD
Spring Hill, Florida

Kapisthalam (KS) Kumar, MD
Trinity, Florida

Shachar Peles, MD
Lake Worth, Florida

Zanetta S Lamar, MD
Naples, Florida

Syed F Zafar, MD
Fort Myers, Florida

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Agenda

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Drs Bekaii-Saab and Philip

Module 5 — Chronic Lymphocytic Leukemia: *Drs Chanan-Khan and Kahl*

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ER-Positive Breast Cancer Faculty

Harold J Burstein, MD, PhD
Institute Physician
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Komal Jhaveri, MD
Associate Attending Physician
Breast Medicine Service and Early Drug Development Service
Section Head
Endocrine Therapy Research Program
Clinical Director
Early Drug Development Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
Associate Professor of Medicine
Weill Cornell College of Medicine
New York, New York

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Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

BWH BRIGHAM AND WOMEN'S HOSPITAL

ER positive Breast Cancer

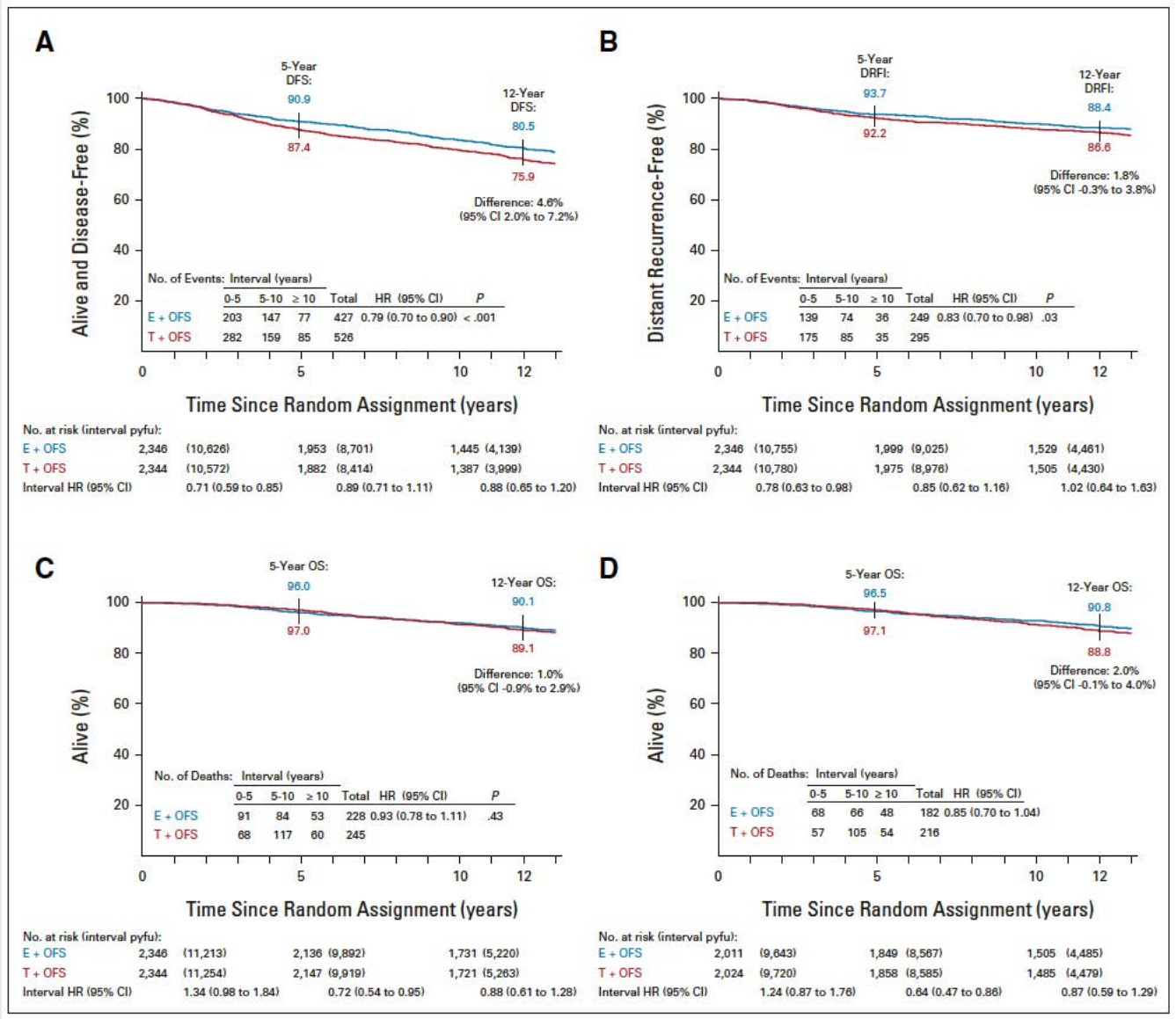
Harold J. Burstein, MD, PhD

@drhburstein

hburstein@partners.org

Early-stage breast cancer

Long-Term Follow-Up of the Combined TEXT and SOFT Trials: Outcomes After a 13-Year Median Follow-Up



(A) Disease-free survival (DFS)

(B) Distant recurrence-free interval (DRFI)

(C) Overall survival (OS) distributions in the ITT population

(D) OS in the predominant subgroup with HER2-negative cancers

Pagani O et al. *J Clin Oncol* 2023 March 1;41(7):1376-82.

E = exemestane; OFS = ovarian function supression; T = tamoxifen; ITT = intent to treat

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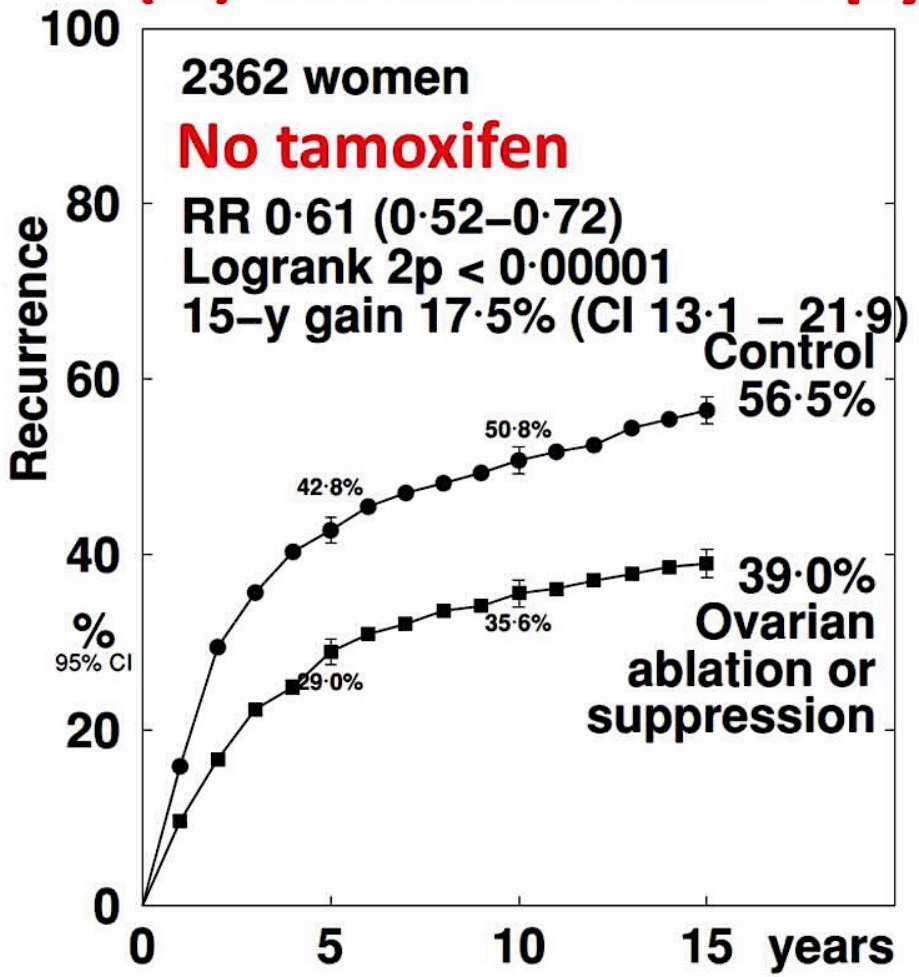
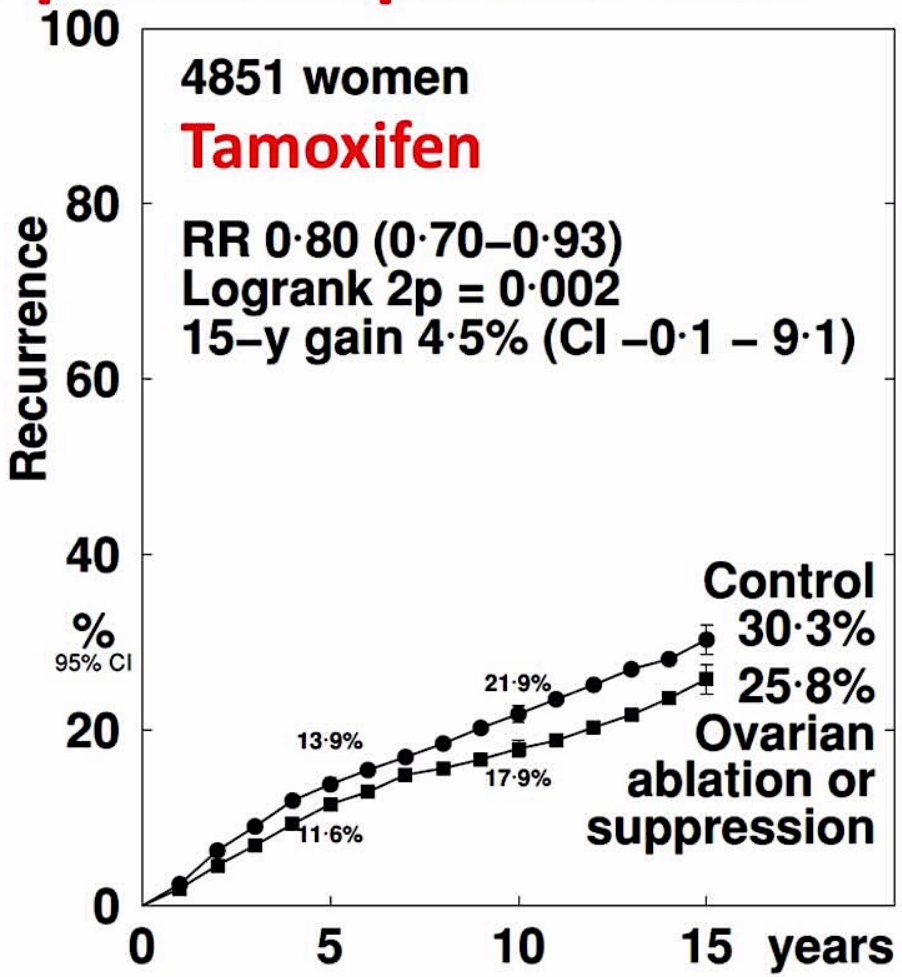
Ovarian ablation/suppress. vs not: Recurrence by tamoxifen use

(A) No chemotherapy or premenopausal after



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	8·37 (412 / 4921)	2·22 (82 / 3691)	1·26 (37 / 2945)	1·28 (69 / 5395)
Control	10·82 (427 / 3945)	2·90 (80 / 2757)	2·47 (52 / 2103)	1·37 (52 / 3785)
Rate ratio, from	0·60 CI 0·49 – 0·72	0·66 CI 0·43 – 0·99	0·47 CI 0·27 – 0·81	0·85 CI 0·51 – 1·42
(O–E) / V	–51·8 / 100·0	–9·6 / 22·8	–9·8 / 12·9	–2·4 / 14·3



Recurrence rates (% / year) and logrank analyses

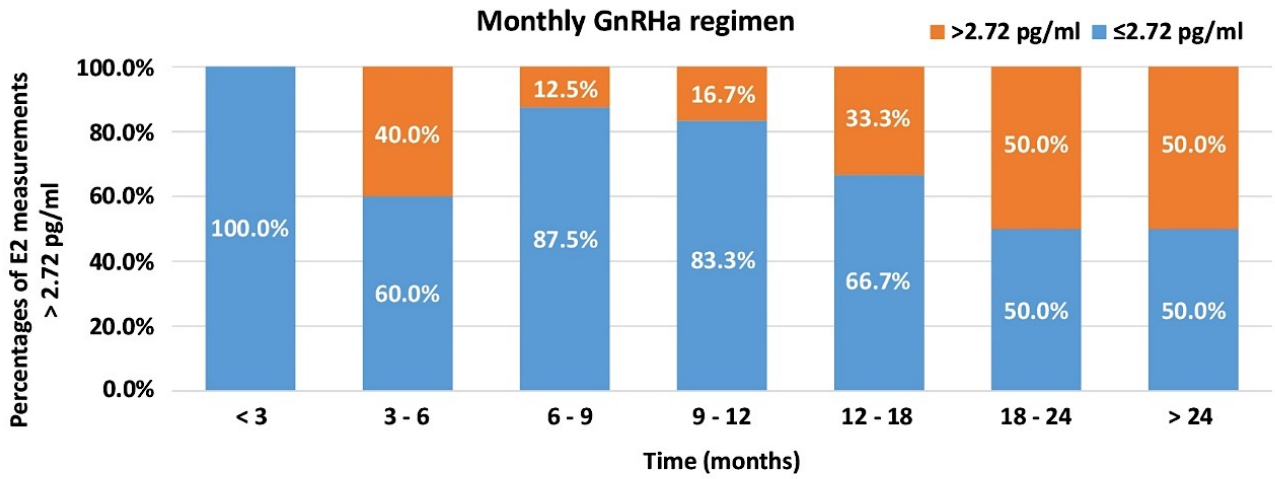
Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	2·47 (255 / 10311)	1·54 (96 / 6242)	1·75 (41 / 2346)	2·40 (3 / 125)
Control	2·98 (313 / 10499)	1·92 (118 / 6159)	2·21 (48 / 2169)	1·85 (2 / 108)
Rate ratio, from	0·81 CI 0·68 – 0·97	0·78 CI 0·58 – 1·03	0·77 CI 0·50 – 1·20	1·94 CI 0·30 – 12·52
(O–E) / V	–26·1 / 126·3	–12·0 / 47·1	–5·0 / 19·7	0·7 / 1·1

Gray RG et al. ASCO 2023;Abstract 503.

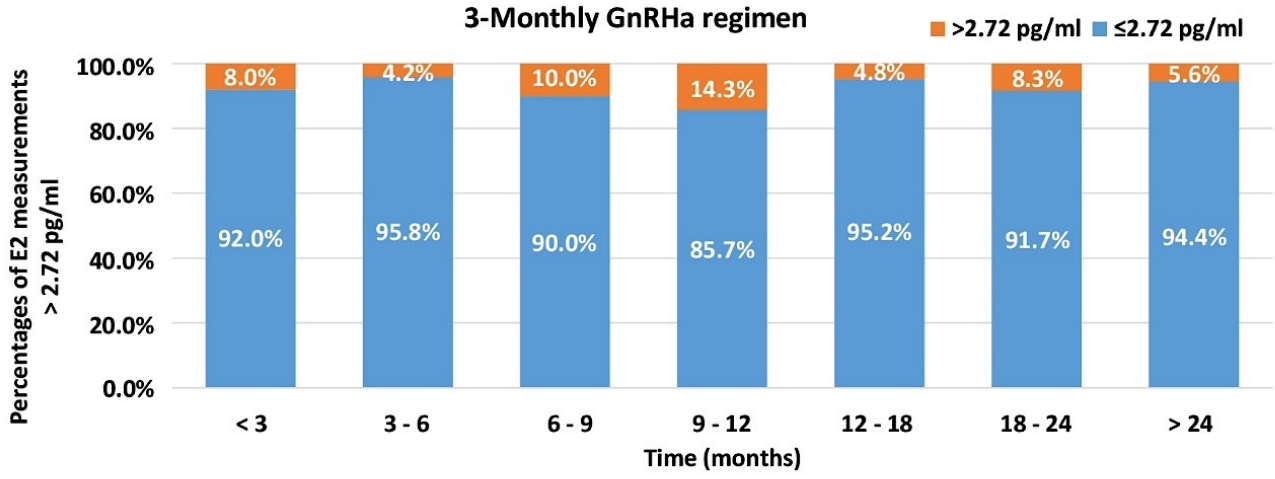
Impact of Ovarian Suppression with GnRH agonists on Fertility Preservation During Chemotherapy

Study	N	Endpoint	Chemo	Chemo + GnRH
Del Mastro JAMA 2011	133	% 1-year amenorrheic	26%	9%
Lambertini JAMA 2015	281	% 5-year premenopausal fxn	64%	72%
Moore NEJM 2015	257	% 2-year ovarian failure	22%	8%

Graphics. Percentages of E2 measurements > 2.72 pg/ml with monthly or 3-monthly GnRHa plus AI at each timepoint during OFS



>2.72 pg/ml	0	4	1	1	3	2	4
≤2.72 pg/ml	6	6	7	5	6	2	4
Total of measurements	6	10	8	6	9	4	8



>2.72 pg/ml	2	1	2	2	1	1	1
≤2.72 pg/ml	23	23	18	12	20	11	17
Total of measurements	25	24	20	14	21	12	18

MonarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

International, Randomized, Open-label Phase III Trial

Women or men with high-risk, node-positive, HR+/HER2- EBC; prior (neo)adjuvant CT permitted; pre- or postmenopausal; no distant metastasis; ≤16 mo from surgery to randomization; ≤12 wk of ET after last non-ET (N = 5637)

ITT Population (Cohorts 1 + 2)

COHORT 1
≥4 positive ALN *or* 1-3 positive ALN + histologic grade 3 and/or tumor ≥5 cm

COHORT 2
1-3 positive ALN, Ki-67 ≥20% per central testing, not grade 3, tumor size <5 cm

STRATIFIED BY PRIOR CT, MENOPAUSAL STATUS, REGION

Abemaciclib 150 mg BID up to 2 yr + **ET** per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2808)

ET per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2829)

Primary Endpoint: iDFS

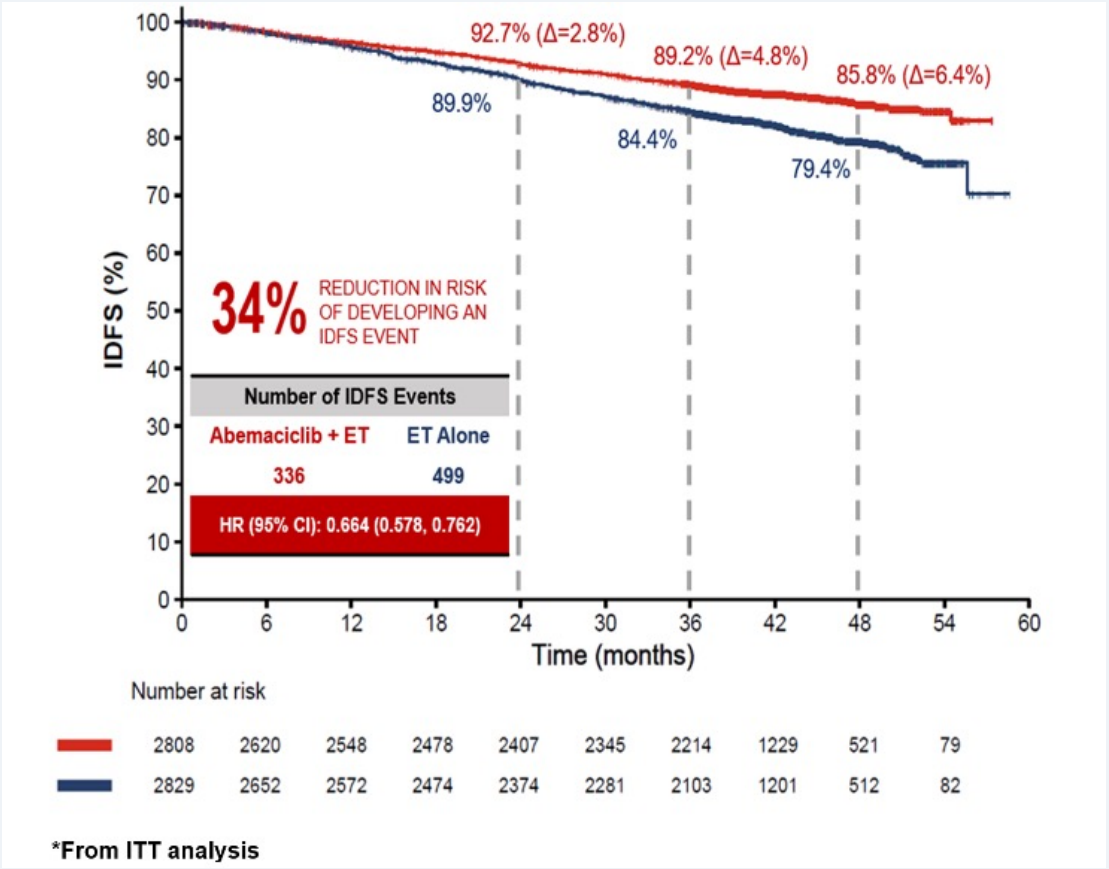
- Planned for after ~390 iDFS events (~85% power; assumed iDFS hazard ratio: 0.73; cumulative 2-sided α = 0.05)
- Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population

Key Secondary Endpoints: iDFS in Ki-67 high (≥20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987.

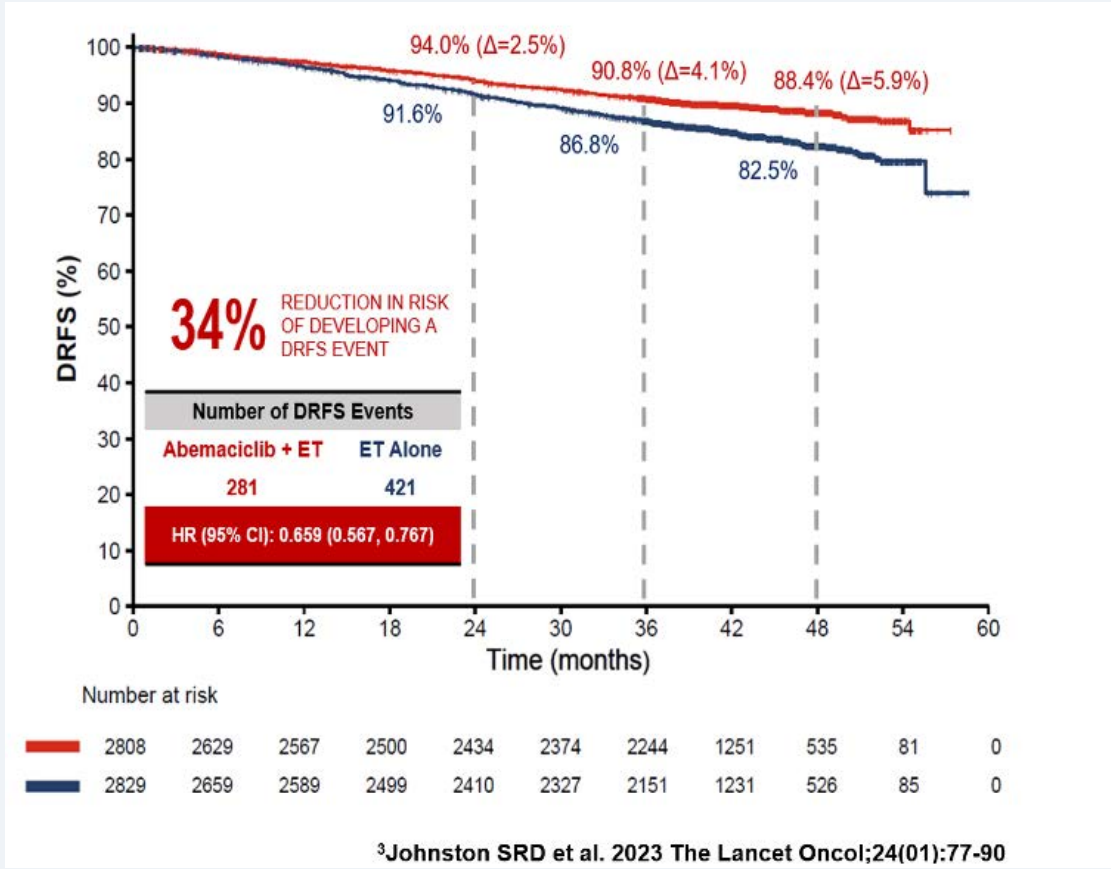
IDFS and DRFS Benefit at 4 Years

IDFS



*From ITT analysis

DRFS

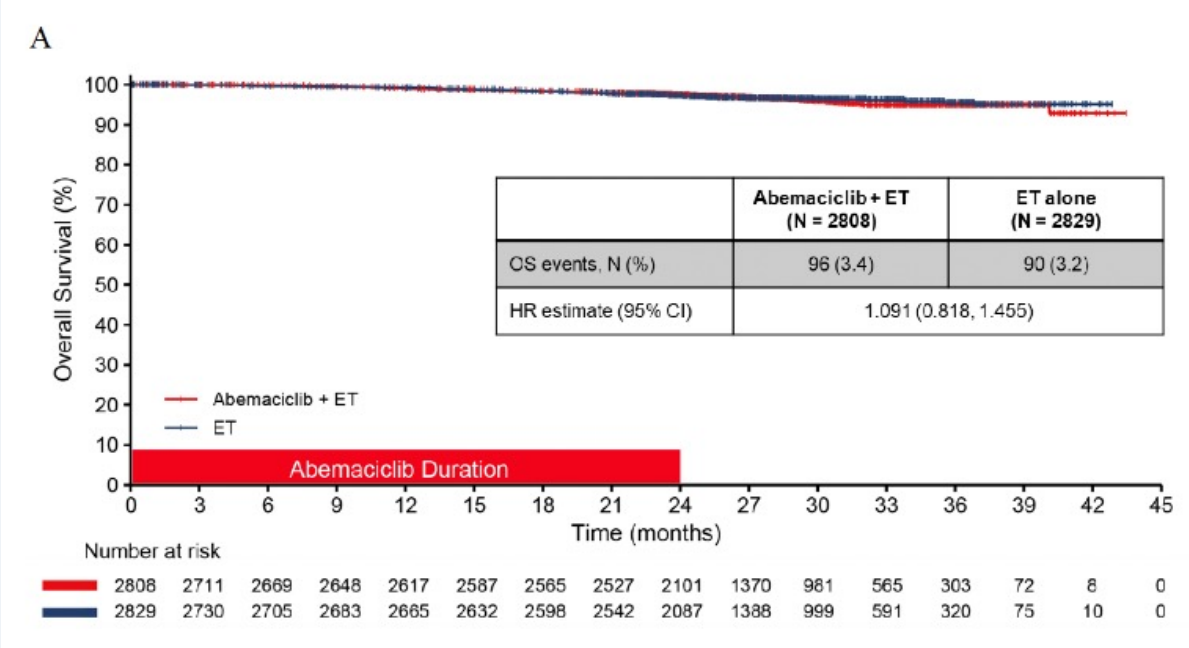


[3]Johnston SRD et al. 2023 The Lancet Oncol;24(01):77-90

Hamilton, ASCO 2023.

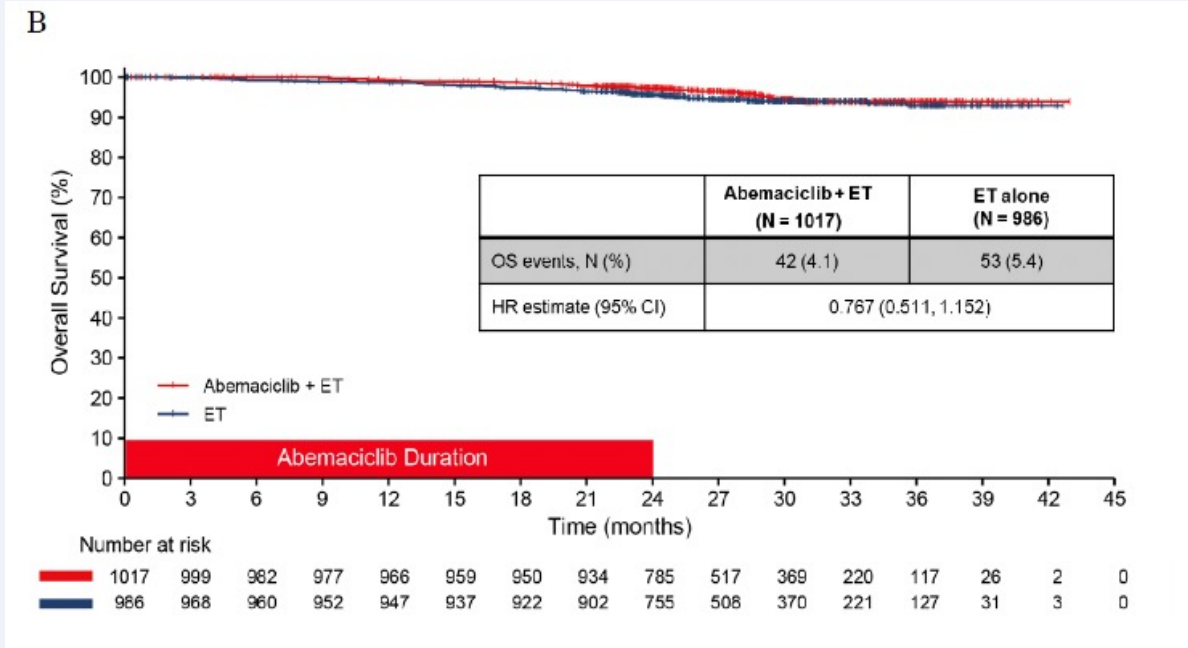
Overall Survival Data, Median 27m

ITT Population



	Abemaciclib + ET (N = 2808)	ET alone (N = 2829)
OS events, N (%)	96 (3.4)	90 (3.2)
HR estimate (95% CI)	1.091 (0.818, 1.455)	

Ki-67 High Population

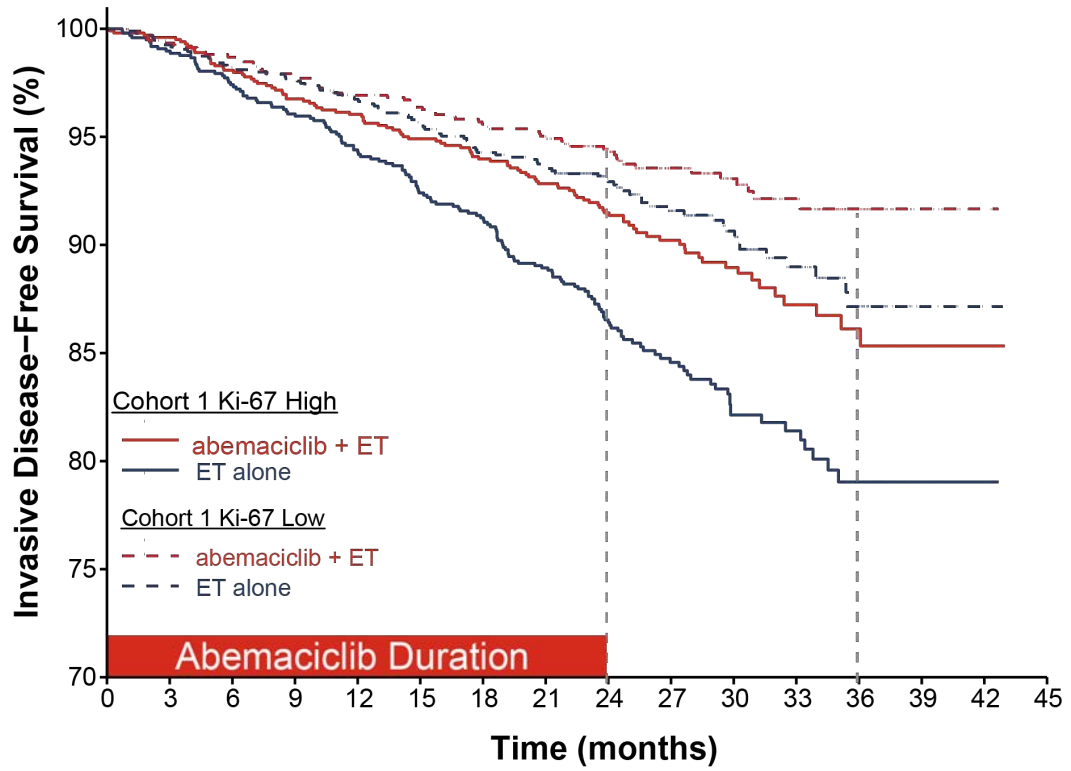


	Abemaciclib + ET (N = 1017)	ET alone (N = 986)
OS events, N (%)	42 (4.1)	53 (5.4)
HR estimate (95% CI)	0.767 (0.511, 1.152)	

➔ Comparable Number Of Deaths In Both Study Arms (3.4% Vs 3.2%)

Harbeck N, et al. *Ann Oncol*. 2022;33:227-228.

Ki-67 is Prognostic, Not Predictive of Abemaciclib IDFS Benefit



	Abemaciclib + ET	ET alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

Ki-67 is prognostic

Ki-67 is not predictive of abemaciclib benefit

Absolute Benefit of Abemaciclib 7.1% in Hi-67 High Group Versus 4.5% in the Ki-67 Low Group

O'Shaughnessy ESMO Plenary 2022.

NATALEE study design[1,2]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

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Letrozole or anastrozole[d] for ≥ 5 y
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Primary End Point
- iDFS using STEEP criteria

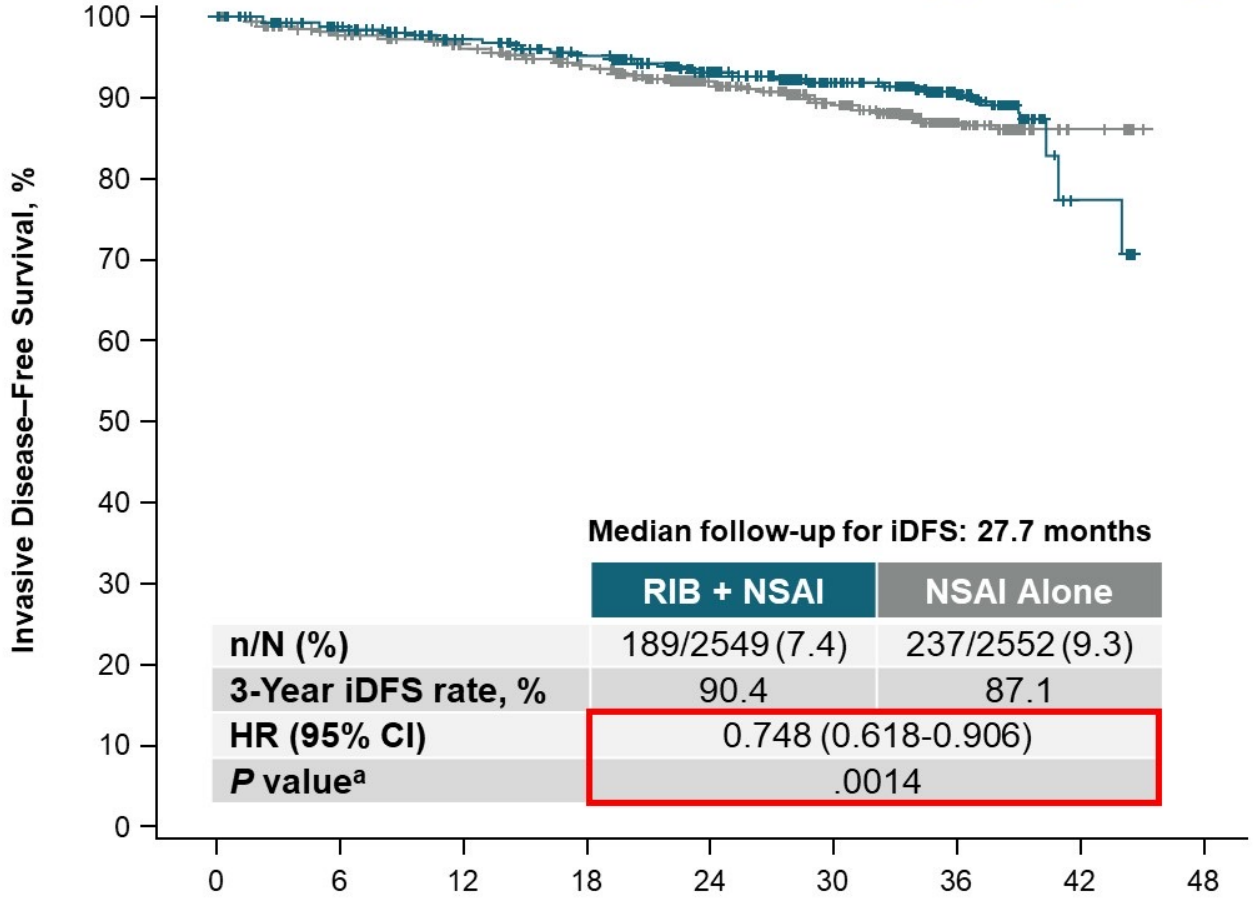
Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597].

Ribociclib achieved highly significant iDFS benefit



Median follow-up for iDFS: 27.7 months

	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
***P* value[a]**	.0014	

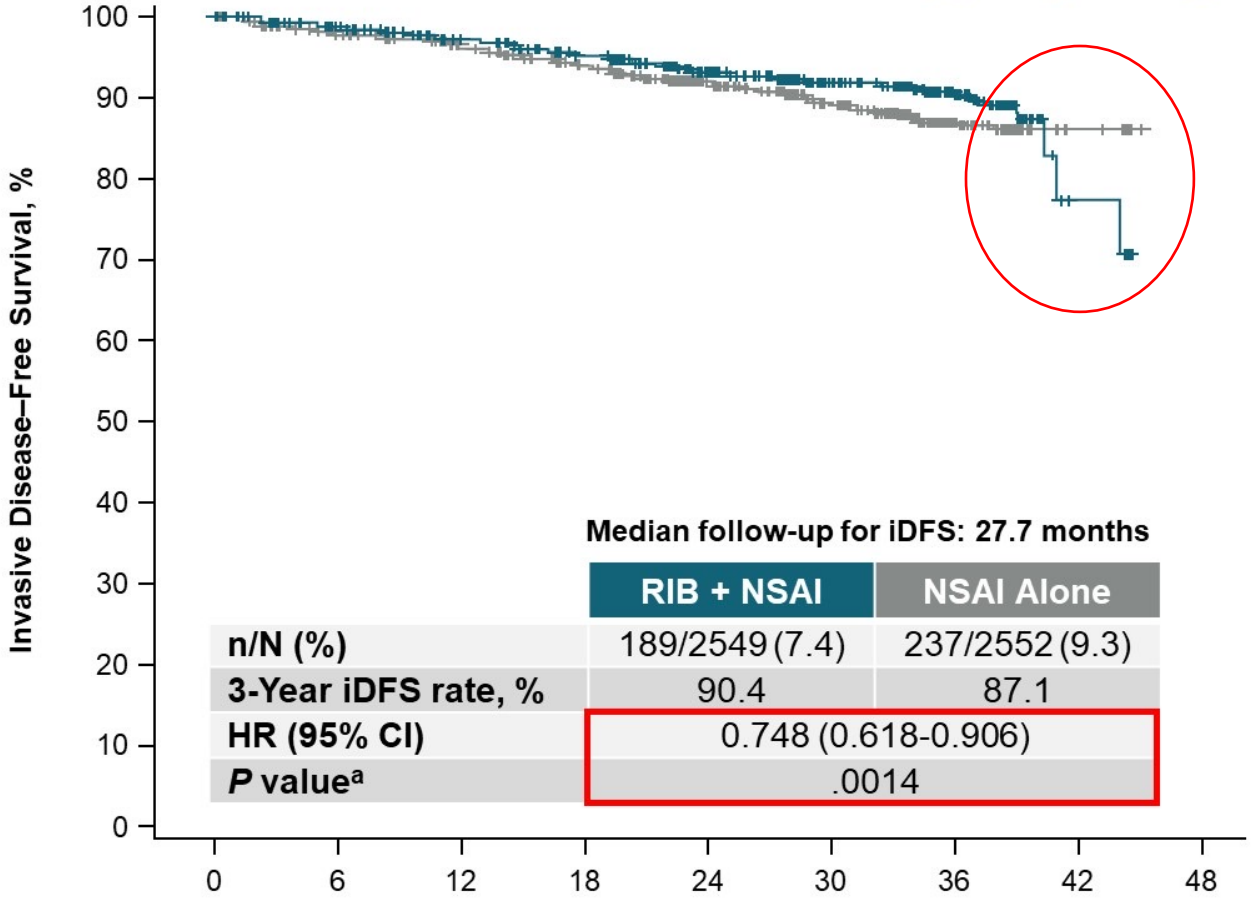
No. at risk

RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

- Based on the *P* value of .0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Ongoing patients will remain on treatment and follow-up will continue as prespecified

iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

Ribociclib achieved highly significant iDFS benefit



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iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

Ribociclib at the 400-mg dose was safe and well tolerated

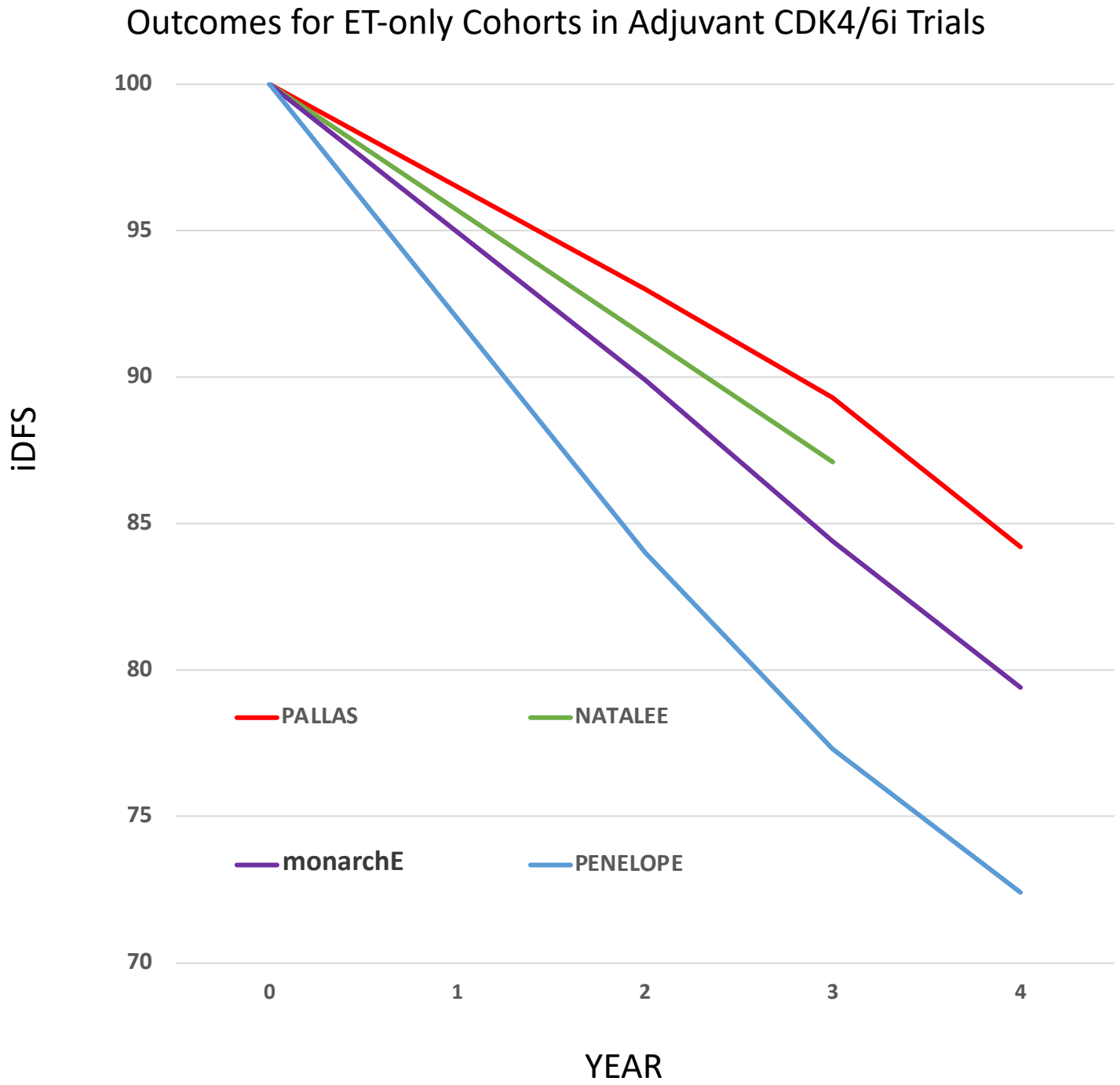
	RIB + NSAI n = 2524		NSAI Alone n = 2444	
AESIs, %	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Neutropenia[a]	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	25.4	8.3	10.6	1.5
QT interval prolongation[c]	5.2	1.0	1.2	0.5
ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis[d]	1.5	0	0.8	0.1
Other clinically relevant AEs,%				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

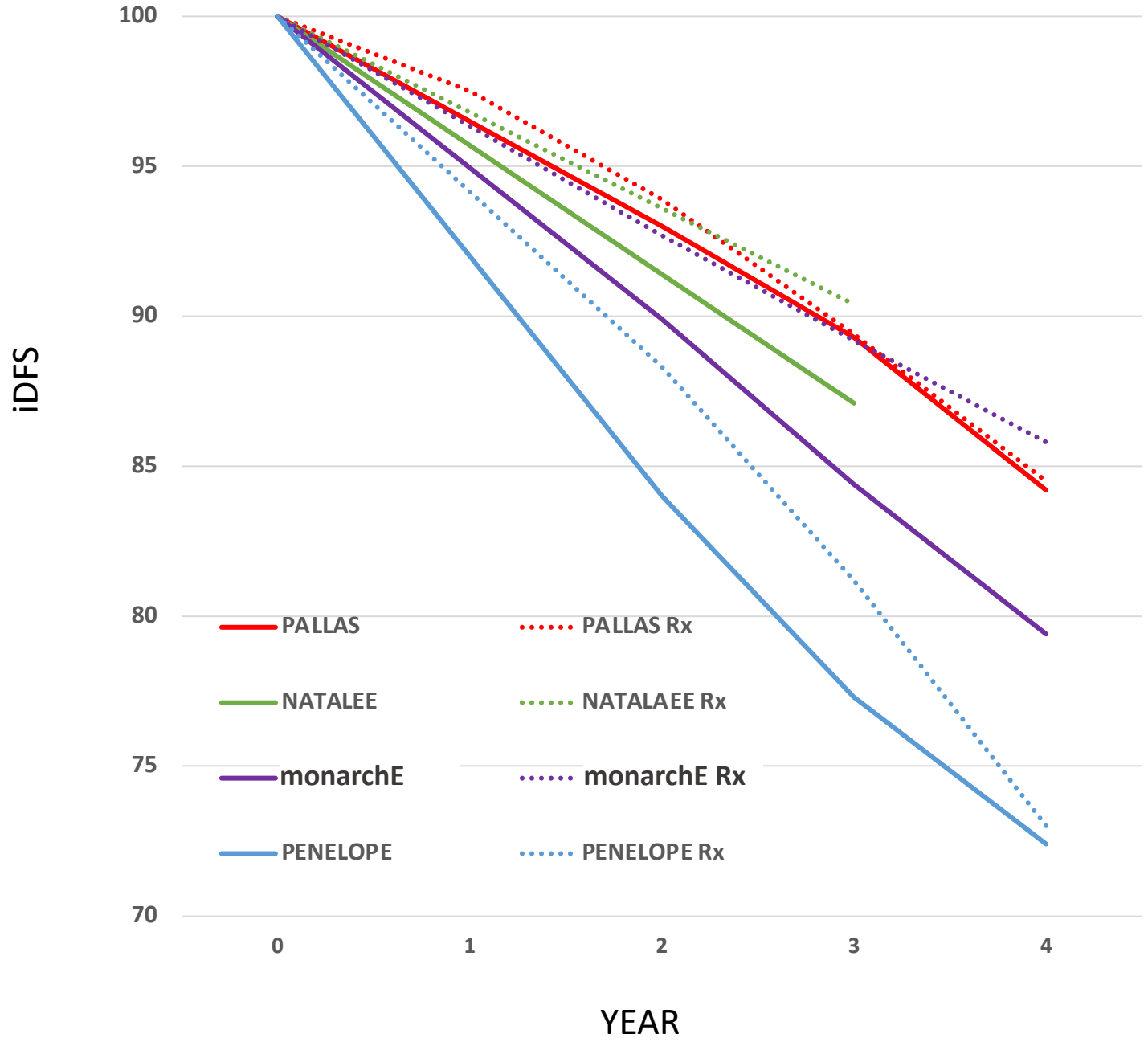
- The most frequent all-grade AEs (RIB + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of RIB occurred early in treatment
  - Median time of these discontinuations was 4 months

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease.

Studies differ by:

Agent
Eligibility
Baseline risk
Treatment duration
Available follow-up
Rx schedule
Endocrine partner




100
95
90
85
80
75
70
iDFS
PALLAS
PALLAS Rx
NATALEE
NATALAEE Rx
monarchE
monarchE Rx
PENELOPE
PENELOPE Rx
0
1
2
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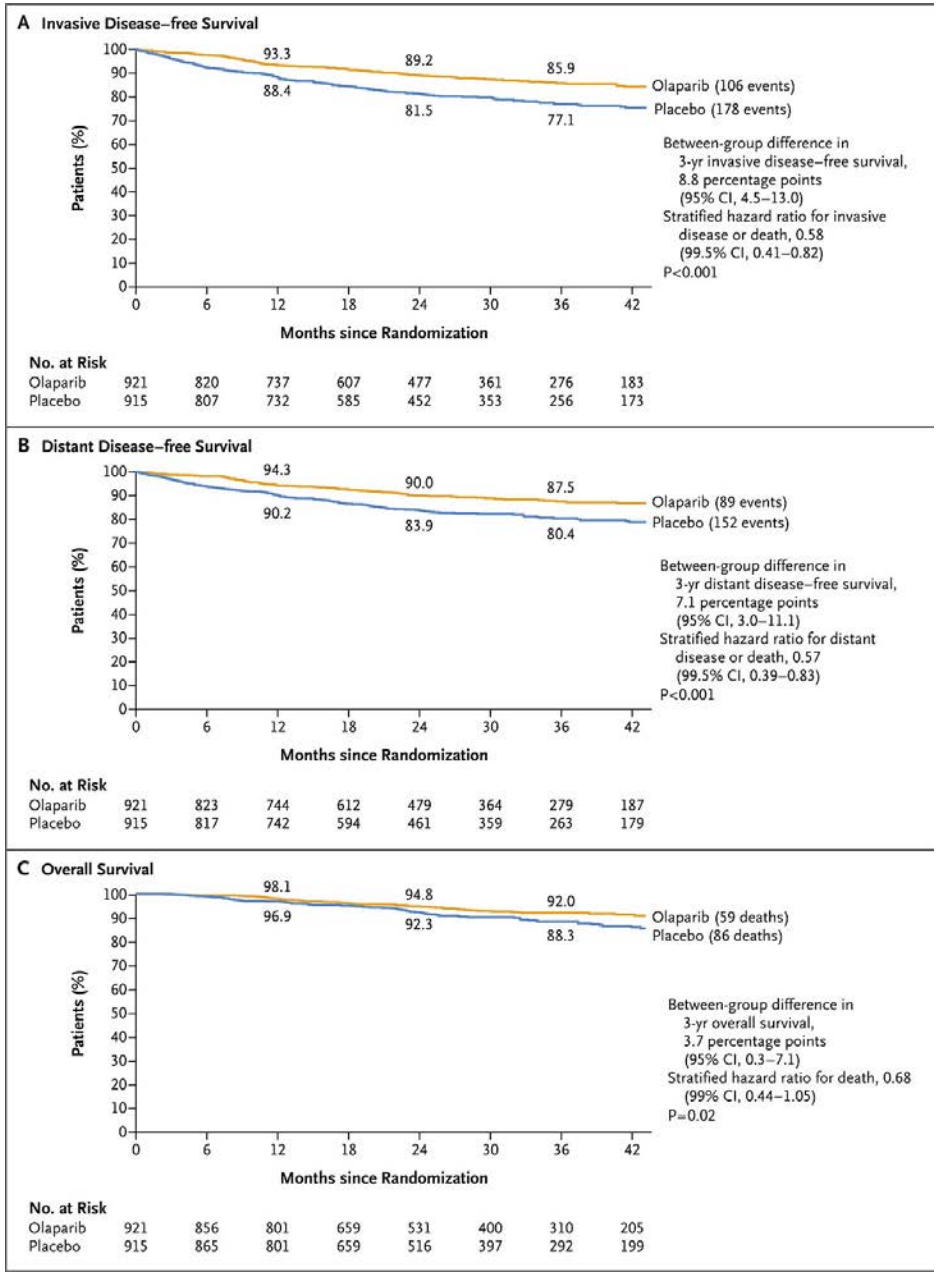
YEAR

OlympiA Trial: Adjuvant Olaparib in BRCA1/2-associated Localized Breast Cancer



Treatment: one year of olaparib

AN Tutt et al. N Engl J Med 2021;384:2394-2405.

OlympiA: Comparison of Efficacy Results at Data Cutoffs 1 and 2

	Prior IA IDFS analysis Median follow-up 2.5 years	Current IA2 OS analysis Median follow-up 3.5 years
IDFS hazard ratios (CI)	*0.58 (99.5% CI: 0.41, 0.82)*	0.63 (95% CI: 0.50, 0.78)
P value needed for significance	*0.005*	N/A
P value observed at analysis	*< 0.0001*	N/A
Difference in IDFS rate (CI)	*3 Yr. 8.8% (95% CI: 4.5, 13.0)*	3 Yr. 8.8% (95% CI: 5.0, 12.6) 4 Yr. 7.3% (95% CI: 3.0, 11.5)
DDFS hazard ratios (CI)	*0.57 (99.5% CI: 0.39, 0.83)*	0.61 (95% CI: 0.48, 0.77)
P value needed for significance	*0.005*	N/A
P value observed at analysis	*< 0.0001*	N/A
Difference in DDFS rate (CI)	*3 Yr. 7.1% (95% CI: 3.0, 11.1)*	3 Yr. 7.0% (95% CI: 3.5, 10.6) 4 Yr. 7.4% (95% CI: 3.6, 11.3)
OS hazard ratios (CI)	***0.68 (99% CI: 0.44, 1.05)***	0.68 (98.5% CI: 0.47, 0.97)
P value needed for significance	***0.010***	0.015
P value observed at analysis	***0.024***	0.009
Difference in OS rate (CI)	***3 Yr. 3.7%*** *(95% CI: 0.3, 7.1)*	3 Yr. 3.8% (95% CI: 0.9, 6.6) 4 Yr. 3.4% (95% CI: -0.1, 6.8)

IA = interim analysis; IDFS = invasive disease-free survival; DDFS = distant disease-free survival; OS = overall survival

Tutt ANJ et al. ESMO Virtual Plenary 2022;Abstract VP1-2022; Geyer CE Jr et al. *Ann Oncol* 2022 December;33(12):1250-68.

Press Release (July 28, 2023): Phase 3 KEYNOTE-756 Trial Met Primary Endpoint of Pathological Complete Response (pCR) Rate in Patients With High-Risk, Early-Stage ER+/HER2- Breast Cancer

Pembrolizumab plus chemotherapy before surgery significantly improved pCR rate compared to neoadjuvant placebo plus chemotherapy

KEYNOTE-756 is the first positive Phase 3 study with an immunotherapy regimen to demonstrate a statistically significant improvement in pCR rate in the neoadjuvant setting for this patient population

Today [it was] announced that the pivotal Phase 3 KEYNOTE-756 trial investigating pembrolizumab in combination with chemotherapy met one of its dual primary endpoints of pathological complete response (pCR) rate following the neoadjuvant part of the neoadjuvant/adjuvant study regimen in patients with high-risk, early-stage estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) breast cancer. At a prespecified interim analysis conducted by an independent Data Monitoring Committee (DMC), the pembrolizumab-based regimen demonstrated a statistically significant improvement in pCR rate compared to neoadjuvant placebo plus chemotherapy. A pCR is defined as a lack of all signs of cancer in tissue samples analyzed following completion of neoadjuvant therapy and definitive surgery.

https://www.businesswire.com/news/home/20230728643725/en/Merck-Announces-Phase-3-KEYNOTE-756-Trial-Met-Primary-Endpoint-of-Pathological-Complete-Response-pCR-Rate-in-Patients-With-High-Risk-Early-Stage-ERHER2--Breast-Cancer

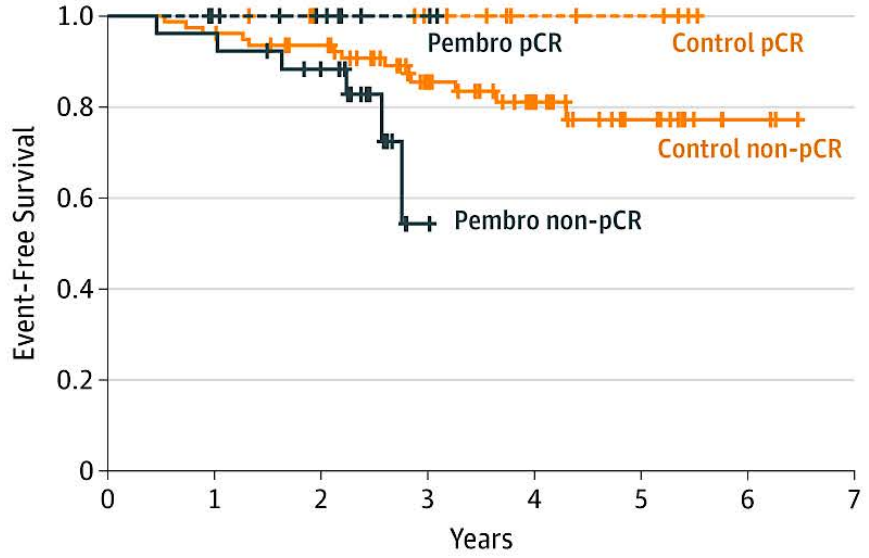
JAMA Network™

From: **Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial**

JAMA Oncol. 2020;6(5):676-684. doi:10.1001/jamaoncol.2019.6650

Neoadjuvant T → AC w/w/o pembrolizumab
pCR estimate without pembro: 13%
pCR estimate with pembro: 30%

C Hormone receptor-positive *ERBB2* negative



No. at risk

Control non-pCR	78	75	69	45	27	13	3	0
Control pCR	14	14	11	9	5	4	0	0
Pembro non-pCR	26	25	20	1	0	0	0	0
Pembro pCR	12	10	7	2	0	0	0	0

Control

	Event	No.	Hazard Ratio
Non-pCR	13	78	1 [Reference]
pCR	0	14	0

Pembro

	Event	No.	Hazard Ratio
Non-pCR	6	26	1 [Reference]
pCR	0	12	0.28

Table 3. Systemic therapy for ER-positive HER2-negative breast cancer

Anatomic stage	TN	Type and duration of endocrine therapy[a]	Ovarian suppression	Chemotherapy[b]/abemaciclib		Olaparib
				Premenopausal	Postmenopausal	Premenopausal and postmenopausal
Stage I	T1ab N0	AI or Tam, 5 years[c]	No OFS	No	No	No
	T1c N0	AI or Tam, 5 years	Consider OFS and AI/Tam for higher risk, particularly those warranting chemotherapy, age <40 years, high grade, or intermediate genomic scores (e.g. recurrence score 16-25)	Consider no chemotherapy for favorable biology tumors especially if not pursuing OFS[d] Yes for less favorable biology tumors	No for favorable biology tumors[d] Yes for less favorable biology tumors	No
Stage II	N0 (node negative)	Consider extended therapy[e], especially after initial 5 years of tamoxifen	OFS and AI/Tam for higher risk, particularly those warranting chemotherapy, age <40 years, high grade, or intermediate genomic scores (e.g. recurrence score 16-25)	Consider chemotherapy for favorable biology tumors especially if not pursuing OFS[d] Yes for less favorable biology tumors	No for favorable biology tumors[d] Yes for less favorable biology tumors	No
	N1 (1-3+ LN)	Extended therapy[e]	OFS and AI/Tam	Consider for favorable biology tumors[d] Yes for less favorable biology tumors Abemaciclib for 2 years	No for favorable biology tumors[d] Yes for less favorable biology tumors Abemaciclib for 2 years for high-risk stage II	No[f]
Stage III		Extended therapy[e]	OFS and AI/Tam	Yes Abemaciclib for 2 years	Yes Abemaciclib for 2 years	Yes for patients with ≥4 pathologically confirmed positive lymph nodes in the adjuvant setting Yes for patients ER and/or PgR-positive/HER2-negative with residual invasive cancer in the breast and/or the resected lymph nodes (non-pCR) and a CPS and EG score ≥3.

Curigliano G, et al.
St Gallen Consensus 2023
Annals of Oncology 2023 online

Advanced breast cancer: CDK4/6i

RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

Ribociclib
(600 mg, 3 weeks on/1 week off)
+
Letrozole or anastrozole + goserelin

Investigators' choice of combination CT[e]

Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

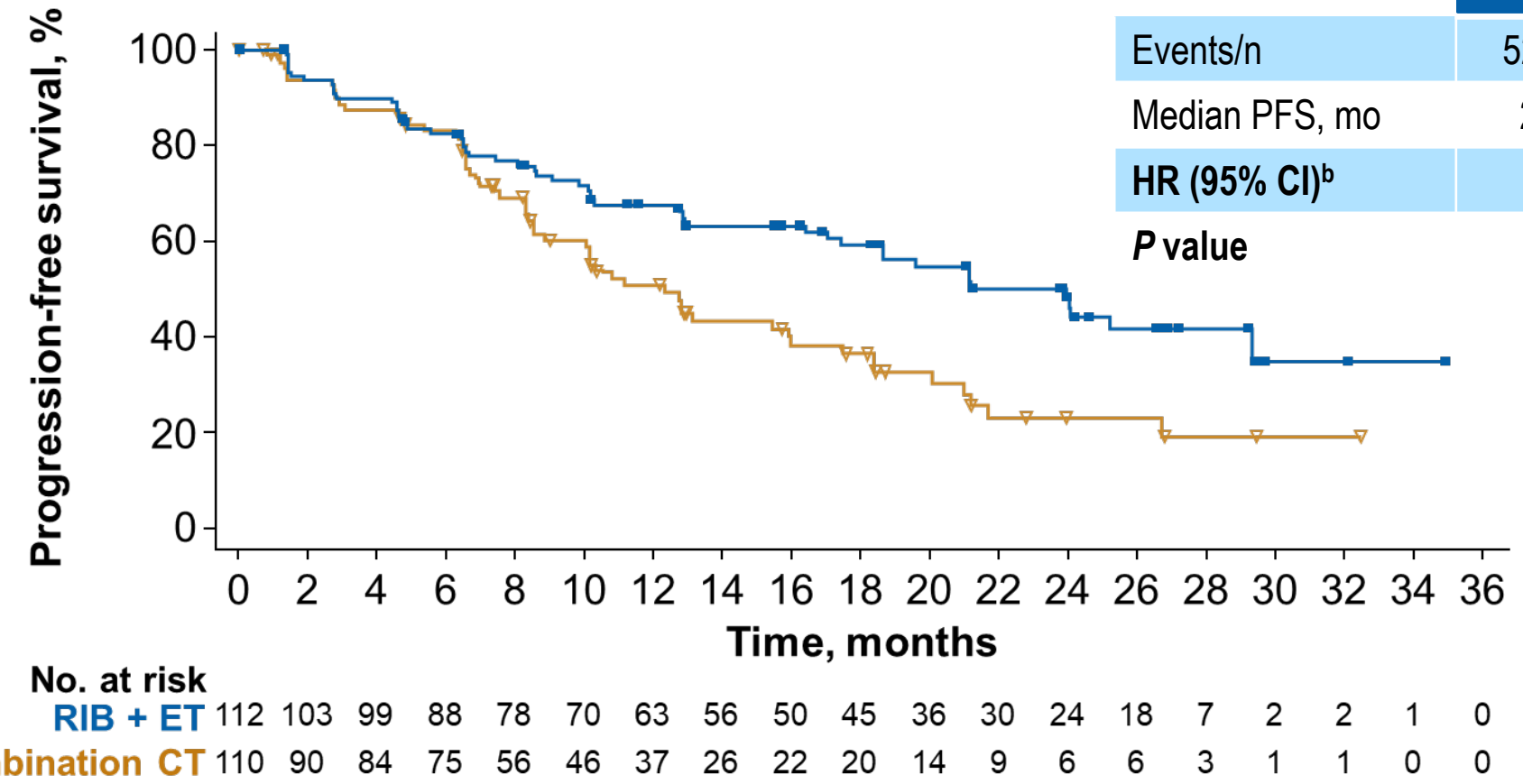
Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.

[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

First-line RIB + ET achieved a statistically significant PFS benefit of ≈ 1 year over combination CT in aggressive HR+/HER2− ABC

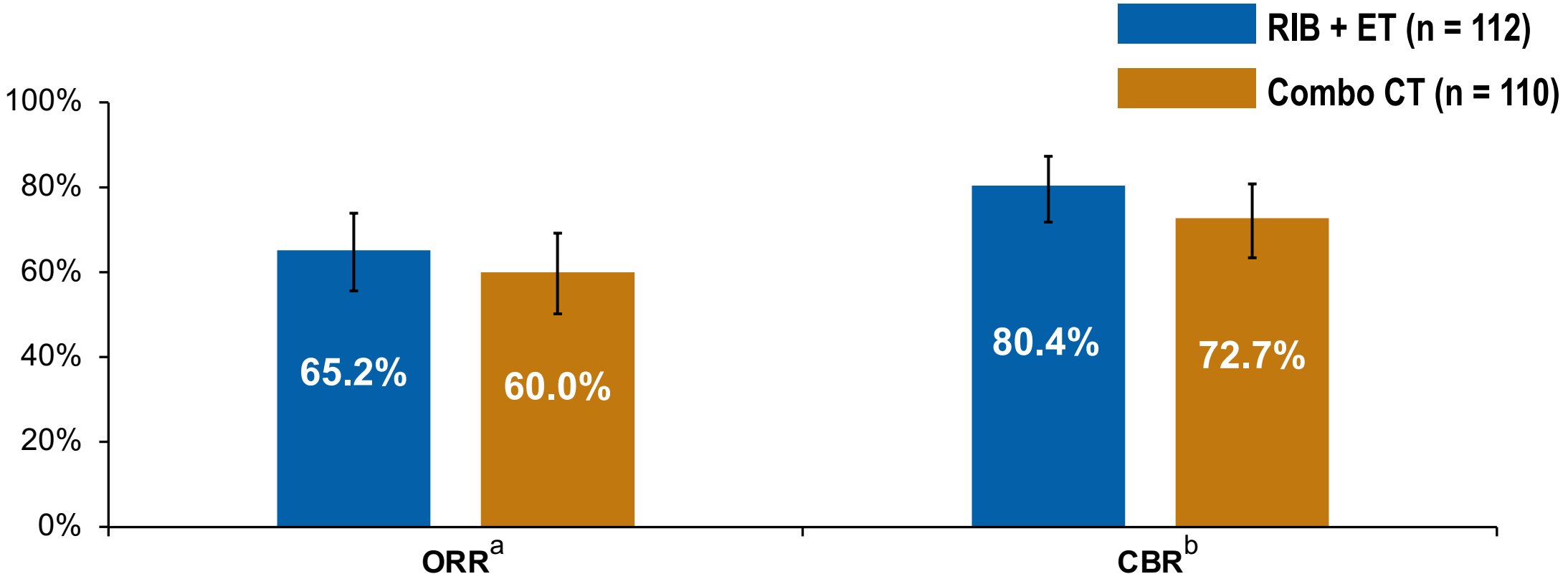


	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; IRT, interactive response technology; PFS, progression-free survival; RIB, ribociclib.

[a] Ten patients in CT arm did not receive any treatment; [b] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT.

ORR and CBR were similar between RIB + ET and combination CT



- A sensitivity analysis[c] confirmed the ORR and CBR findings in the safety set

CBR, clinical benefit rate; Combo CT, combination chemotherapy; CR, complete response; ET, endocrine therapy; ORR, overall response rate; PD, progressive disease; PR, partial response, RIB, ribociclib; SD, stable disease.
[a] Proportion of patients with CR or PR without confirmation (confirmation imaging was not mandatory according to study protocol); [b] Proportion of patients with CR or PR without confirmation or SD or non-CR/non-PD ≥24 weeks; [c] This analysis included all patients who received ≥1 dose of any component of the study treatment (safety set).

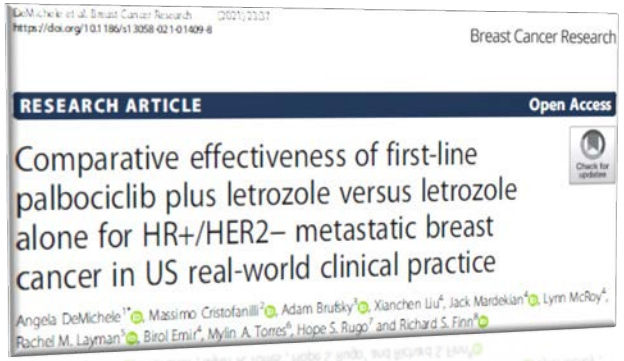
CDK4/6 Inhibitors + Endocrine Therapy Improve PFS in the 1st/2nd line MBC Setting

Study/Arms	[1]PALOMA-1	[2]PALOMA-2	[3]MONALEESA-2	[4]MONARCH 3	[5]MONALEESA-7	[6]PALOMA-3	[7]MONARCH 2	[8]MONALEESA-3
Phase	2	3	3	3	3	3	3	3
CDK4/6i ET partner	Palbo AI	Palbo AI	Ribo AI	Abema AI	Ribo AI/Tam + OS	Palbo Fulvestrant	Abema Fulvestrant	Ribo Fulvestrant
N	165	666	668	493	642	521	669	726
Median PFS (months) Placebo	10.2	14.5	16	14.8	13.0	4.6	9.3	12.8
Median PFS (months) CDK 4/6i	20.2	27.6	25.3	28.1	23.8	11.2	16.4	20.5
HR 95% CI	0.48 0.31-0.74	0.56 0.46-0.69	0.54 0.41-0.69	0.54 0.42-0.70	0.55 0.44-0.69	0.50 0.40-0.62	0.553 0.45-0.68	0.593 0.480-0.732
P value	<0.01	<0.01	<0.01	0.000002	<0.01	<0.01	<0.01	<0.01

[1]Finn R, et al. Lancet Oncol. 2015; 16:25-35; [2]Rugo H, et al, et al. SABCS. 2017; [3]Hortobagyi GN, et al. ASCO; [4]Johnston S, et al. NPJ Breast Cancer 2019 Jan 17:5:5; [5]Tripathy D, et al. Lancet Oncol. 2018 Jul;19(7):904-915. [6]Turner NC, et al. N Engl J Med. 2015;373:209-219; [7]Sledge GW, et al. JCO. 2017;35:2875-2884; [8]Slamon DJ, et al. J Clin Oncol. 2018 Aug 20;36(24):2465-2472.

CDK4/6 Inhibitors + Endocrine Therapy Improve OS in the 1st/2nd line MBC Setting

Study/Arms	MONALEESA-2	[1]MONALEESA-7	[2]PALOMA-3	[3]MONARCH 2	[4]MONALEESA-3
Phase	3	3	3	3	3
CDK4/6i ET partner	Ribo Letrozole	Ribo AI/Tam + OS	Palbo Fulvestrant	Abema Fulvestrant	Ribo Fulvestrant
N	668	642	521	669	726
ITT Median OS (mo) Placebo	51.4	40.9	28.0	37.3	41.5
ITT Median OS (mo) CDK 4/6i	63.9	NE	34.9	46.7	53.7
HR 95% CI, P value	0.76 0.63-0.93; p=0.004	0.71 0.54-0.95; p=0.00973	0.81 0.64-1.03, p=0.09	0.757 0.606-0.945, p=0.01	0.73 0.730-0.90, p=0.00455


Breast Cancer Research

RESEARCH ARTICLE Open Access

Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2– metastatic breast cancer in US real-world clinical practice

Angela DeMichele[1*], Massimo Cristofanilli[2], Adam Brufsky[3], Xianchen Liu[4], Jack Mardekian[4], Lynn McRoy[4], Rachel M. Layman[5], Birol Emir[4], Mylin A. Torres[6], Hope S. Rugo[7] and Richard S. Finn[8]

[1]Im et al, NEJM 2019; [2]Turner et al, NEJM 2019; [3]Sledge et al, JAMA Oncol 2019; [4]Neven et al, ESMO Breast 2022

Comparative overall survival (OS) of CKD4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) in advanced breast cancer

Authors: Coralea Kappel, Mitchell Elliott, Vikaash Kumar, Michelle B. Nadler, Alexandra Desnoyers, Eitan Amir

UNIVERSITY OF TORONTO

Background:

- CDK4/6i and ET are an international gold standard therapy in ER+ HER2- advanced breast cancer
- Individual trials of abemaciclib, palbociclib and ribociclib show similar impact on PFS yet differing statistical significance for OS
- A robust comparative evaluation of the efficacy, safety, and tolerability of the three drugs is warranted.

Methods:

- Search of PubMed, ASCO, ESMO and SABCS for phase 3 RCTs reporting OS of CDK4/6i in combination with ET in ER+ aBC in 1L or 2L
- A network meta-analysis using WinBUGS was performed to evaluate comparative efficacy and toxicity based on the ET partner.
- Efficacy comprised assessment of OS while for safety and tolerability we included treatment discontinuation without progression, treatment-related death and commonly reported adverse events (AEs).
- Where possible AEs were assessed individually based on CTCAE-reported grade.

Conclusions/Main Findings:

- No statistically significant difference in OS between the different CDK4/6 inhibitors.
- Significant differences between CDK4/6i were observed for safety and tolerability outcomes.

ASCO 2023;Abstract 1056.

Author contact: Coralea.Kappel@uhn.ca

Results/Graphs/Data:

Table 1. Differences in OS between the CDK4/6i with AI or fulvestrant backbone

AI backbone			
Control / Experimental	**Palbociclib**	**Ribociclib**	**Abemaciclib**
Palbociclib	-	0.79 (0.56, 1.14), p = 0.21	0.79 (0.52, 1.19), p = 0.26
Ribociclib	1.26 (0.88, 1.80), p = 0.21	-	0.99 (0.74, 1.33), p = 0.96
Abemaciclib	1.27 (0.84, 1.92), p = 0.26	1.01 (0.70, 1.46), p = 0.96	-
Fulvestrant backbone			
Palbociclib	-	0.90 (0.60, 1.33), p = 0.59	0.93 (0.62, 1.40), p = 0.73
Ribociclib	1.12 (0.75, 1.66), p = 0.59	-	1.04 (0.71, 1.52), p = 0.85
Abemaciclib	1.08 (0.72, 1.61), p = 0.73	0.96 (0.66, 1.42), p = 0.85	-

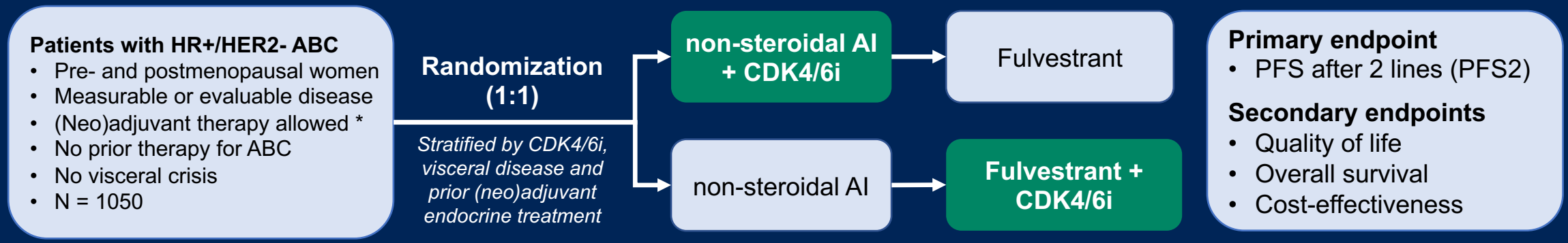
Table 2. Significant AE differences between CDK4/6i with AI or fulvestrant backbone

	With AI			With fulvestrant		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Abemaciclib vs Palbociclib (control)						
Transaminitis grade 3-4	7.55	2.57-22.21	<0.001	2.54	1.0-6.44	0.050
Vomiting grade 1-2	2.27	1.59-3.23	<0.001	1.95	1.37-2.78	<0.001
Diarrhea grade 1-2	7.56	5.48-10.44	<0.001	9.69	6.95-13.49	<0.001
Diarrhea grade 3-4	7.65	3.15-18.55	<0.001	118.06	7.28-1915.32	0.001
Infection grade 3-4	8.54	3.27-22.32	<0.001	4.61	1.76-12.07	0.002
Discontinuation due to AE	1.84	1.2-2.83	0.005	2.49	1.34-4.64	0.004
Ribociclib vs Palbociclib (control)						
Neutropenia grade 3-4	0.4	0.31-0.51	<0.001	0.73	0.55-0.97	0.039
Transaminitis grade 3-4	14.73	5.35-40.52	<0.001	8.94	3.83-20.88	<0.001
Nausea grade 1-2	1.34	1.05-1.72	0.019	1.63	1.22-2.17	0.001
Vomiting grade 1-2	1.87	1.37-2.56	<0.001	1.71	1.2-2.42	0.003
Infection grade 3-4	3.84	1.47-10.01	0.006	5.64	2.19-14.51	<0.001
Abemaciclib vs Ribociclib (control)						
Anemia grade 3-4	1.95	1.09-3.49	0.025	2.44	1.39-4.27	0.002
Neutropenia grade 3-4	0.44	0.33-0.59	<0.001	0.32	0.24-0.42	<0.001
Transaminitis grade 3-4	0.15	0.31-0.85	0.032	0.28	0.17-0.48	<0.001
Diarrhea grade 1-2	6.55	4.87-88	<0.001	6.68	5.01-8.91	<0.001
Diarrhea grade 3-4	6.9	3.34-14.26	<0.001	27.16	8.47-87.14	<0.001
Treatment-related death	2.55	1.05-6.22	0.039	5.01	1.08-23.32	0.040

Future Directions for Research:

- Real-world data analyses may help identify if there is a meaningful inter-drug difference

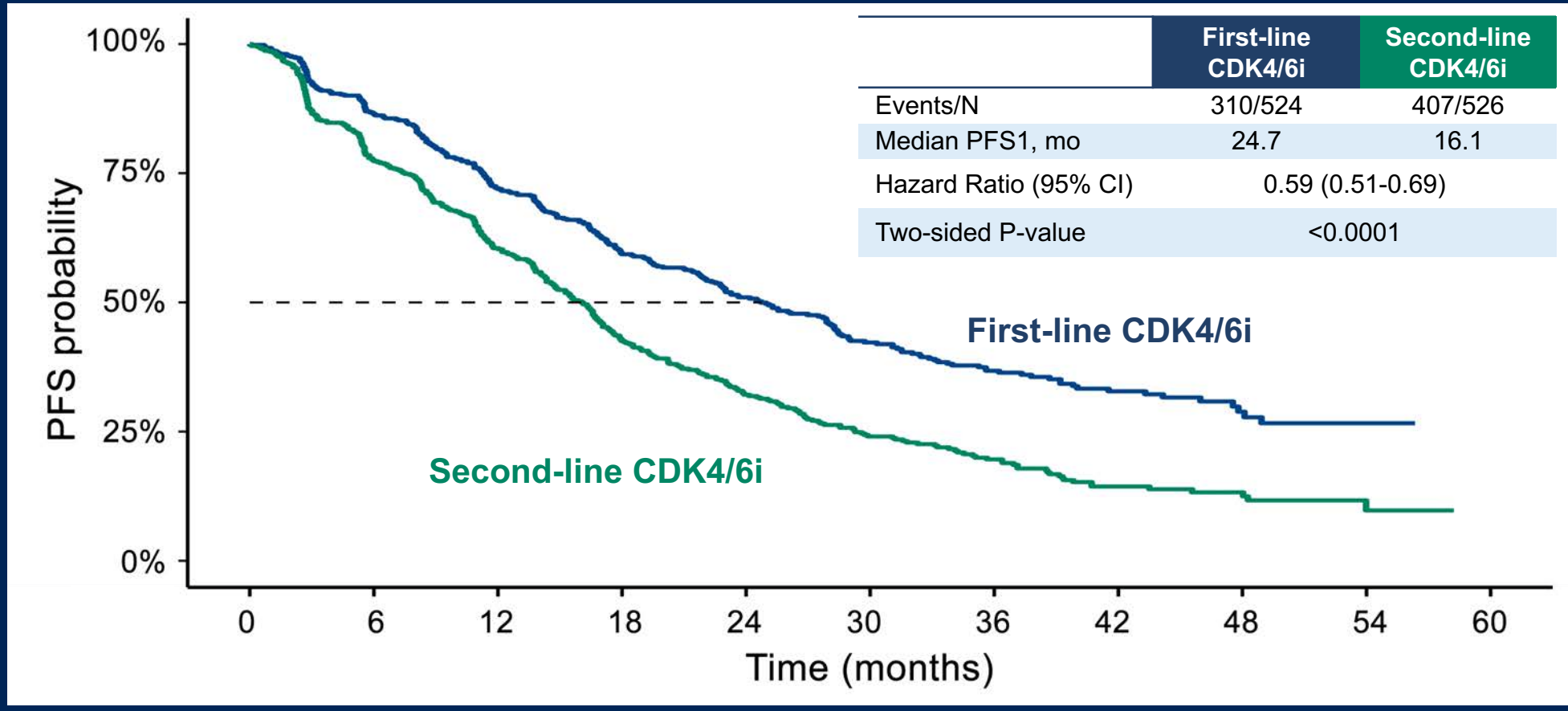
SONIA trial design



- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%
  - 90% received Palbociclib

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. CllinicalTrials.gov (NCT03425838)

PFS1 analysis

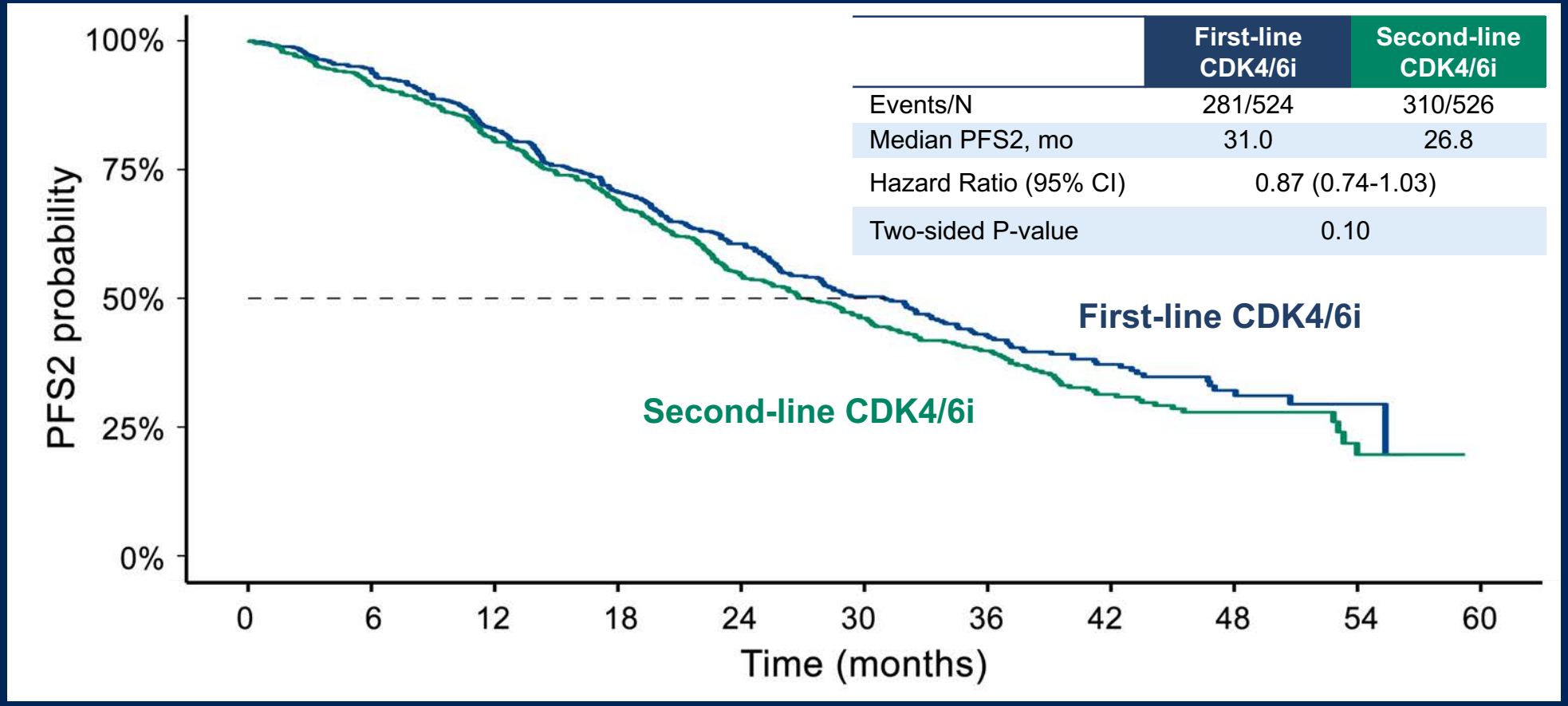


	First-line CDK4/6i	Second-line CDK4/6i
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value	<0.0001	

First-line	524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (210)
Second-line	526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)

Numbers at risk (censored)

PFS2 analysis



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

First-line	524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (315)	5 (239)	0 (243)
Second-line	526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)

Numbers at risk (censored)

Clinical Questions and Cases

Case Presentation: 36-year-old woman with ER/PR-positive, HER2-negative, T3N1 IDC and residual disease (pT2N1A) after neoadjuvant ddAC-T and mastectomy with ovarian suppression and AI is considering CDK

Dr Zanetta Lamar (Naples, Florida; 5-7-2021)

RTP
RESEARCH
TO PRACTICE

Hormone Receptor-Positive Breast Cancer
Introduction: Neoadjuvant Immunotherapy for ER-Positive Disease

- **KEYNOTE-756: Neoadjuvant pembrolizumab/chemotherapy in ER-positive BC (press release and upcoming ESMO presentation)**

Discussion Question

Have you or would you offer an immune checkpoint inhibitor in combination with chemotherapy to a patient with ER-positive, HER2-negative breast cancer to whom you planned to administer neoadjuvant systemic therapy?

Case Presentation: 40-year-old woman with 5.5-cm, ER/PR-positive, HER2-negative, node-positive IDC, s/p bilateral mastectomies, BSO and adjuvant AC-T initiates letrozole/abemaciclib

Dr Susmitha Apuri (Inverness, Florida; 10-14-2021)

RTP RESEARCH TO PRACTICE

Hormone Receptor-Positive Breast Cancer
Endocrine Treatment (Adjuvant, First-Line Metastatic)

- **Adjuvant therapy for premenopausal women**
  - **Tamoxifen monotherapy versus ovarian function suppression**
  - **Ovarian protection with GnRH agonists during chemotherapy**
- **CDK4/6 inhibitors as adjuvant therapy**
- **CDK4/6 inhibitors in metastatic disease**
  - **Choice of first-line CDK4/6 inhibitor**

Discussion Question

A 28-year-old premenopausal woman with a 2.8-cm, ER-positive, HER2-positive IDC who is interested in preserving fertility is going to receive neoadjuvant THP. Would you offer the opportunity to receive a GnRH agonist during neoadjuvant chemotherapy?

Discussion Question

Which adjuvant endocrine treatment would you most likely recommend for a 42-year-old premenopausal patient with a 2-cm, ER-positive, HER2-negative, node-negative IDC and a 21-gene Recurrence Score of 24?

Discussion Question

Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor (in addition to endocrine therapy) to a patient with a 2.8-cm, Grade 2, ER-positive, HER2-negative, node-negative IDC?

Discussion Question

Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor to a patient with a 2.8-cm, Grade 2, ER-positive, HER2-negative IDC with 1 positive axillary node and no other high-risk features?

Discussion Question

What treatment approach would you generally recommend for a 65-year-old patient who presents with de novo ER-positive, HER2-negative breast cancer and symptomatic bone and soft tissue metastases?

RTP
RESEARCH
TO PRACTICE

Discussion Question

Which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy as first-line treatment for a premenopausal woman with de novo ER-positive, HER2-negative metastatic breast cancer?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 59-year-old woman with ER/PR-positive, HER2-negative metastatic breast cancer receives palbociclib/letrozole and is found on liquid biopsy to have a PALB2 mutation

Dr Shaachi Gupta (Lake Worth, Florida; 11-16-2021)

RTP RESEARCH TO PRACTICE

Case Presentation: 62-year-old woman with ER/PR-positive, HER2-negative breast cancer, 8 months s/p adjuvant chemotherapy on an AI is found to have a PALB2 germline mutation

Dr Susmitha Apuri (Inverness, Florida; 10-12-2022)

RTP RESEARCH TO PRACTICE

Hormone Receptor-Positive Breast Cancer
PARP Inhibitors

- Germline and somatic testing
- Role of liquid biopsy
- Adjuvant/postneoadjuvant settings
- Metastatic disease

Discussion Question

A 65-year-old woman with a germline BRCA mutation presents with a 3-cm, Grade 3, ER-positive, HER2-negative localized breast cancer with 3 positive axillary nodes. Would you offer an adjuvant CDK4/6 inhibitor and/or PARP inhibitor as part of treatment?

Discussion Question

Regulatory and reimbursement issues aside, have you attempted or would you attempt to access olaparib as part of adjuvant therapy for a patient with high-risk localized breast cancer and a germline PALB2 mutation?

Selection and Sequencing of Treatment for Relapsed ER-Positive mBC

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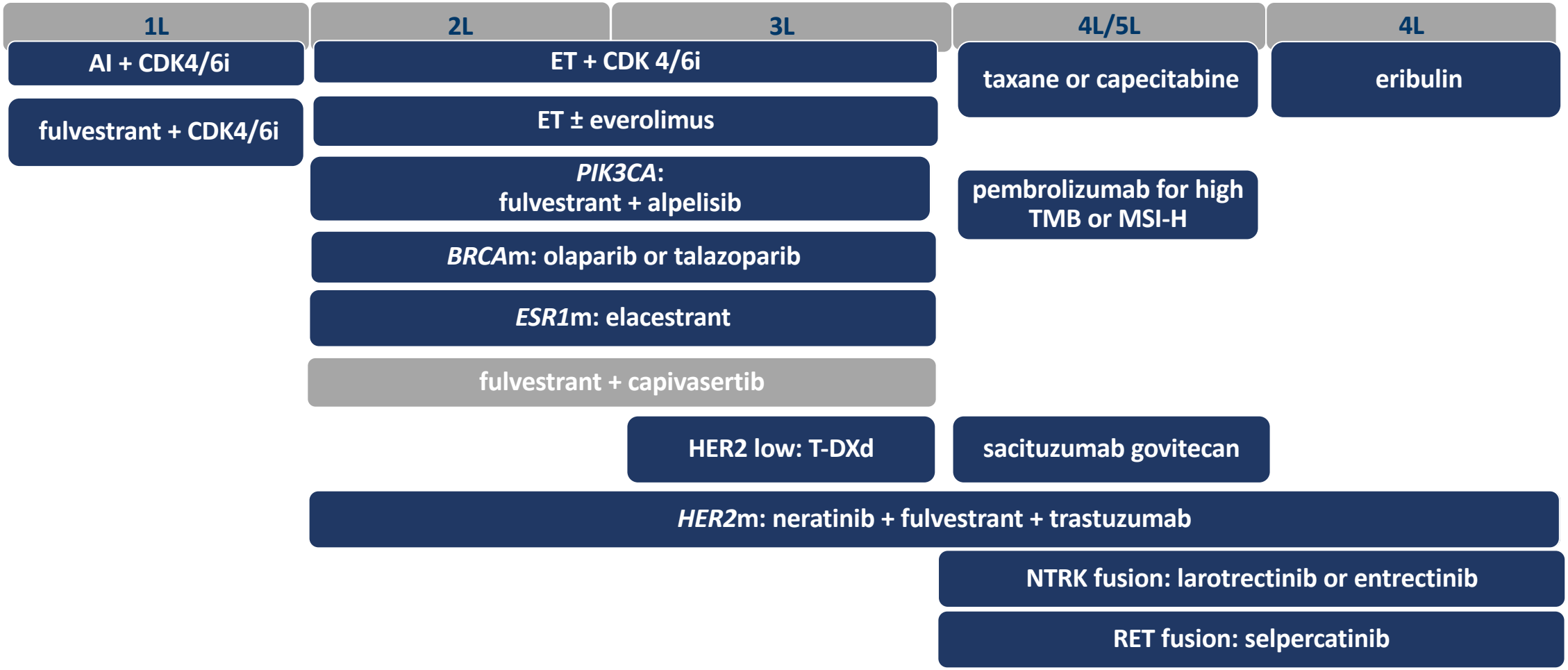
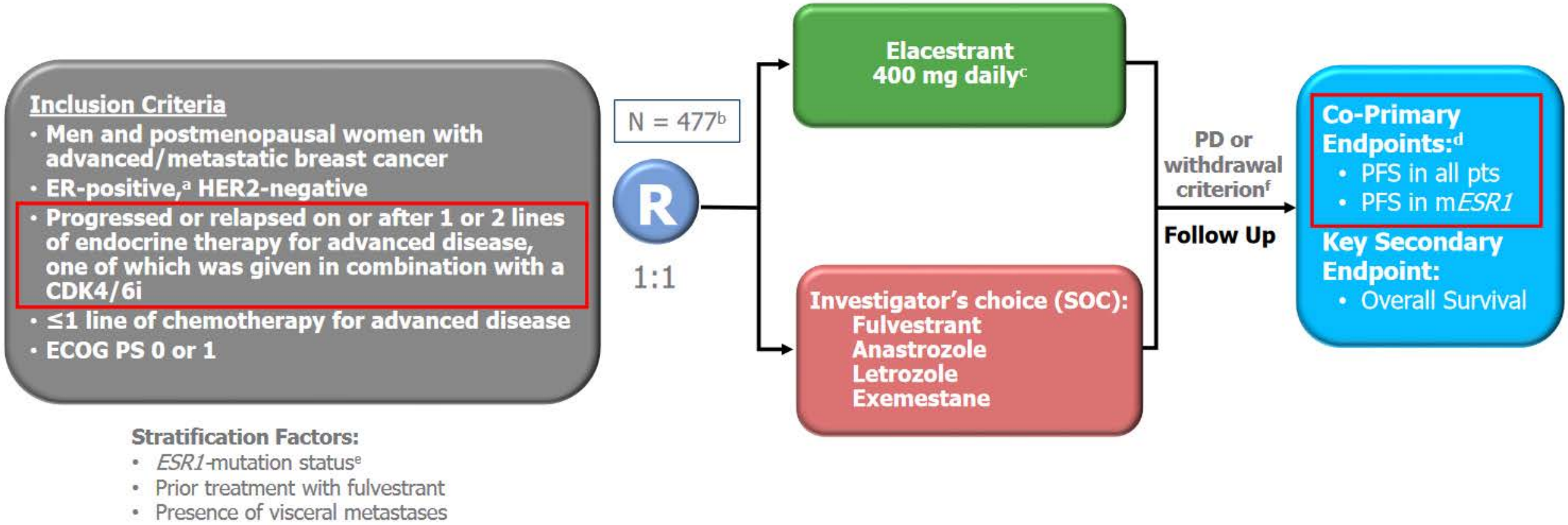
Approach to HR+/HER2- MBC Post-CDK4/6 Inhibitor: Move to Personalization



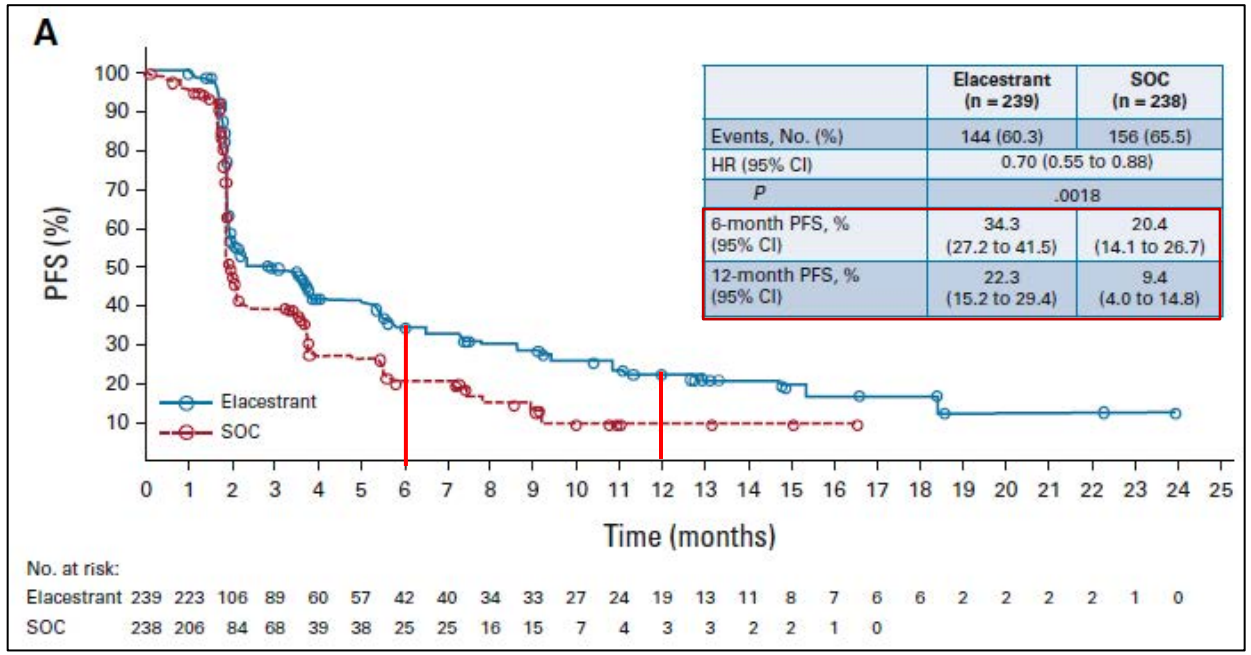
NCCN Clinical Practice Guidelines in Oncology. Breast Cancer V4.2023.
Howell SJ et al. *Lancet Oncol*. 2022;23(7):851-864.

EMERALD: Phase 3 Trial of Elacestrant vs ET in Post CDK4/6i Setting



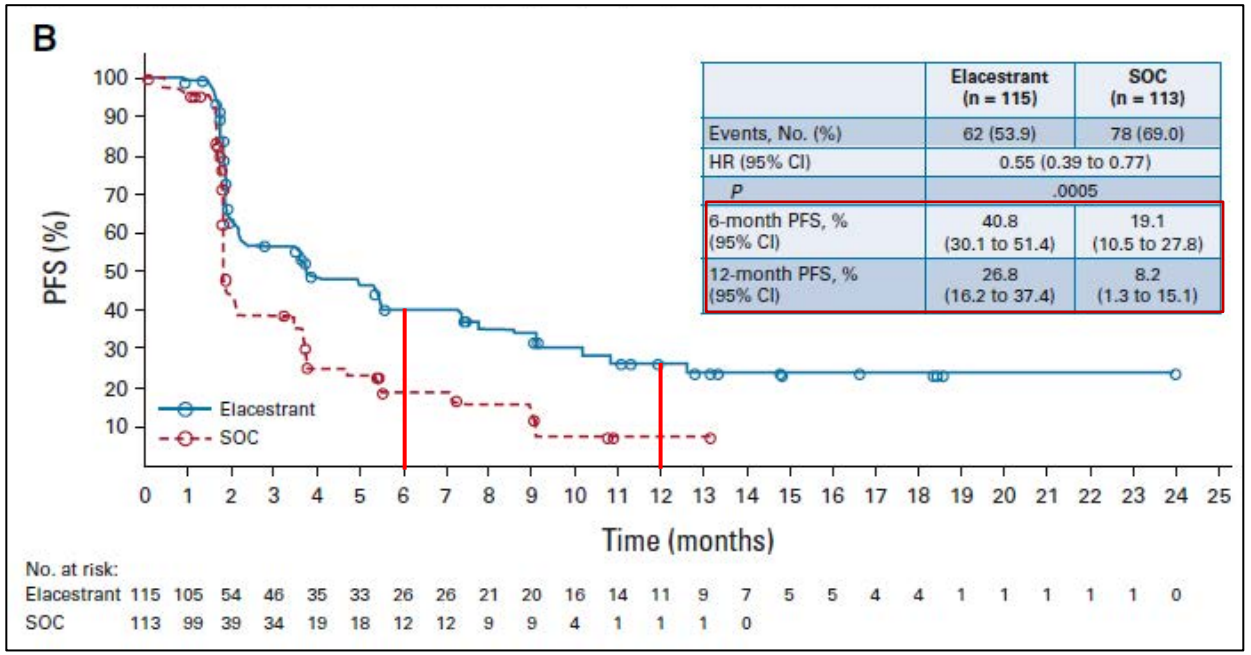
EMERALD Results: Elacestrant vs SOC
PFS Rate at 6 and 12 Months

All Patients



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

Patients with Tumors Harboring *mESR1*

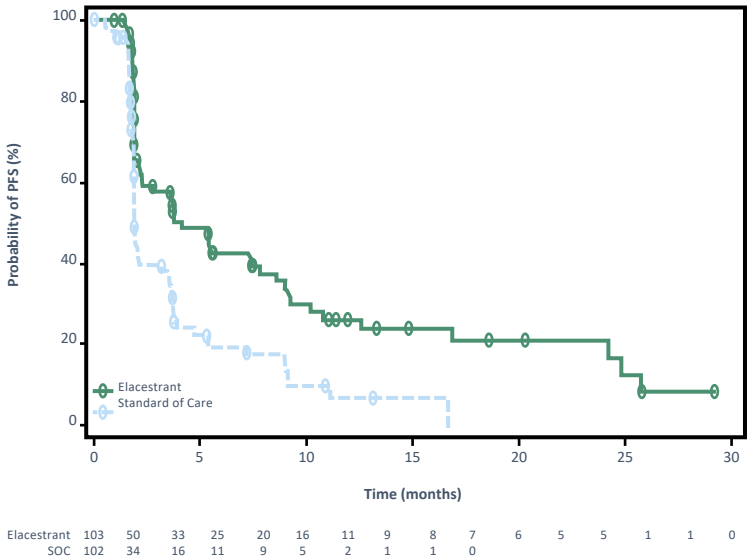


	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

Elacestrant demonstrated improved PFS versus SOC ET in patients with ER+/HER2- advanced/metastatic breast cancer following prior CDK4/6i therapy, particularly in *mESR1* cohort

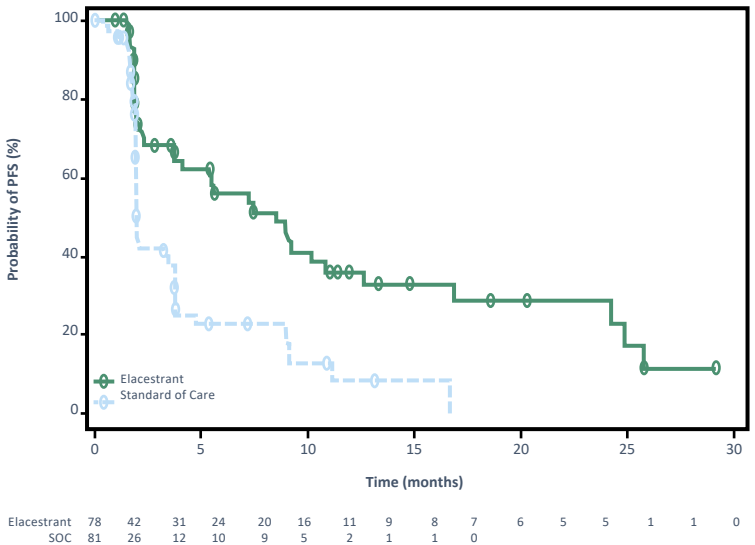
EMERALD Results: Elacestrant vs SOC
PFS by Duration of CDK4/6i in *mESR1* Cohort

≥ 6 Months CDK4/6i



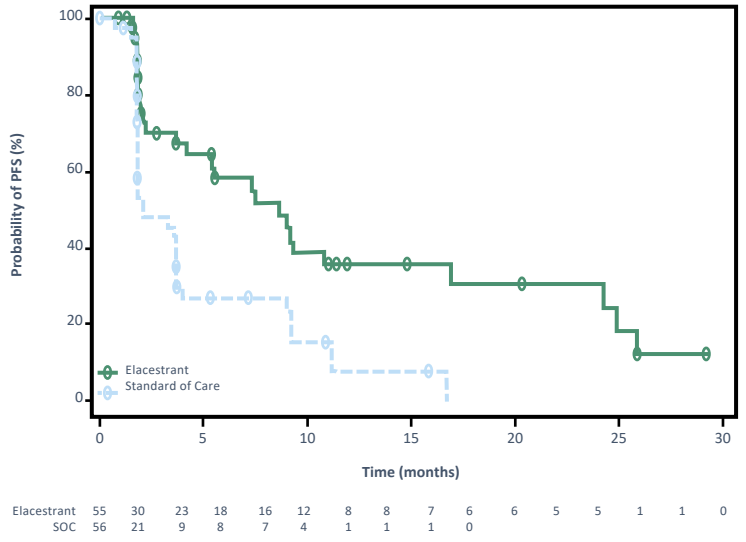
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

≥ 12 Months CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

≥ 18 Months CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Activity of other oral SERDS as monotherapy post CDK4/6i progression

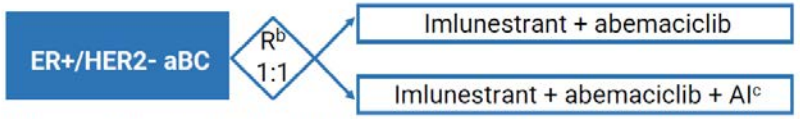
	SERENA-2 (NCT04214288)	EMBER (NCT04188548)
SERD	Camizestrant	Imlunestrant
Phase	2	1
N	288	114
Patient population	ER+/HER2- MBC	ER+/HER2-MBC
Number of prior Therapies	0-2	0-8; median 2
Prior Chemotherapy	19%	27%
Prior Fulvestrant	Not allowed	51%
Prior CDK4/6i	51%	92%
Treatment arms	Camizestrant (various doses) vs Fulvestrant	Imlunestrant (200mg-800mg)
***ESR1* mutations**	37%	49%
Primary endpoint	PFS	Safety, RP2D
Results	phase 3 dose: 75mg QD **PFS 5.5 vs 2.1 months HR 0.49 (prior CDK 4/6i)** **PFS 6.6 vs 2.2 (*ESR1*m) HR 0.33**	RP2D: 400mg QD ORR 8%, CBR 42%; at 400g dose CBR 55%; **PFS in 2L post CDK4/6i 6.5 months**

Oliveira et al SABCS 2022; Jhaveri ASCO 2022

Imlunestrant in combination with Abemaciclib: EMBER Phase 1

Imlunestrant + Abemaciclib +/- AI: N = 85 (Jhaveri SABCS 2022)

Key Inclusion criteria:
- ER+, HER2- aBC
- ≤1 prior therapies for aBC but must not have received a prior CDK4/6 inhibitor
- Demonstrated prior sensitivity to endocrine therapy[a] or have untreated de novo aBC



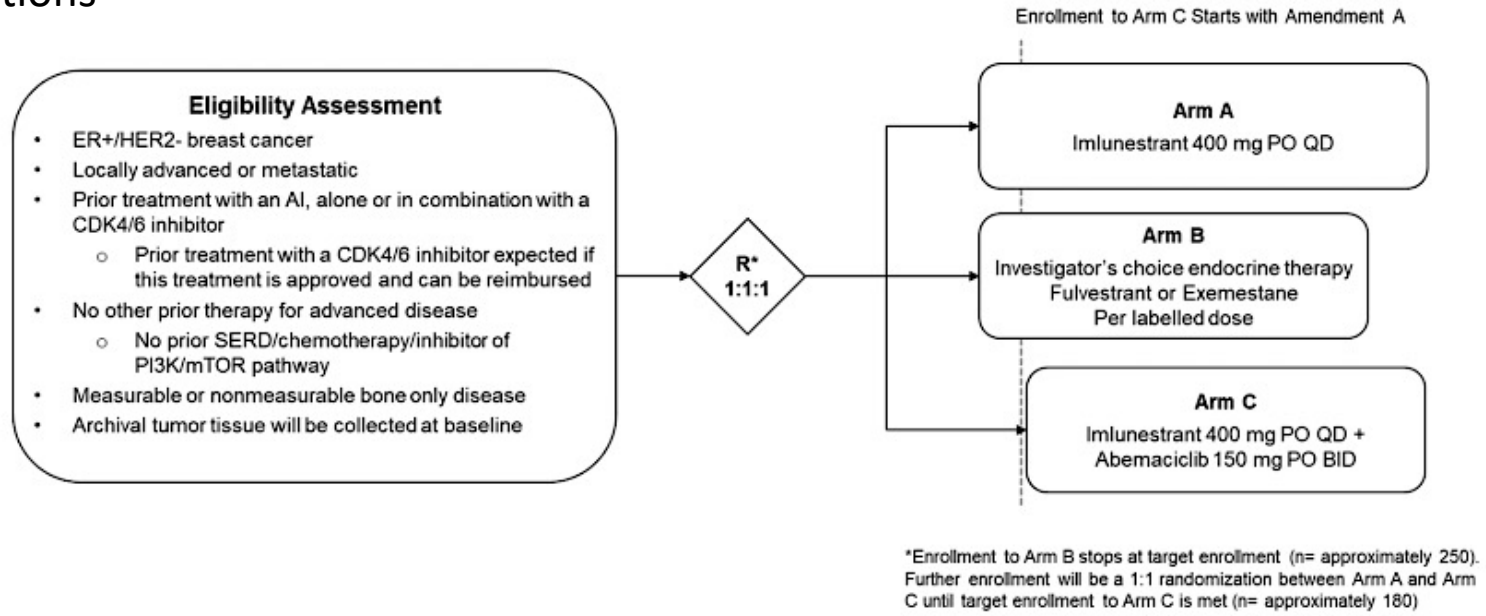
[a] Defined as CR/PR or SD ≥ 24 weeks on ET in advanced setting OR ≥ 24 months on ET in adjuvant setting
[b] Stratified by menopausal status and visceral metastases. Randomization was for enrollment purposes and not for any formal comparison between cohorts.
[c] Physician's Choice AI (Anastrozole, Exemestane, or Letrozole) per label dose and schedule

Table 3. Efficacy parameters in evaluable patients

	Imlunestrant + abemaciclib N=42	Imlunestrant + abemaciclib + AI N=43	Total N=85
ORR, n/N (%)	9/28 (32)	20/34 (59)	29/62 (47)
Median TTR, months (min-max)	3.7 (1.6-10.9)	3.7 (1.7-7.1)	3.7 (1.6-10.9)
CBR, n/N (%)	30/42 (71)	34/43 (79)	64/85 (75)
12-month PFS, %	80	80	80

Safety profile (diarrhea, nausea, fatigue, neutropenia) compared favorably to fulvestrant + Abemaciclib in MONARCH 2
No drug-drug PK interactions

EMBER-3 (NCT04975308)

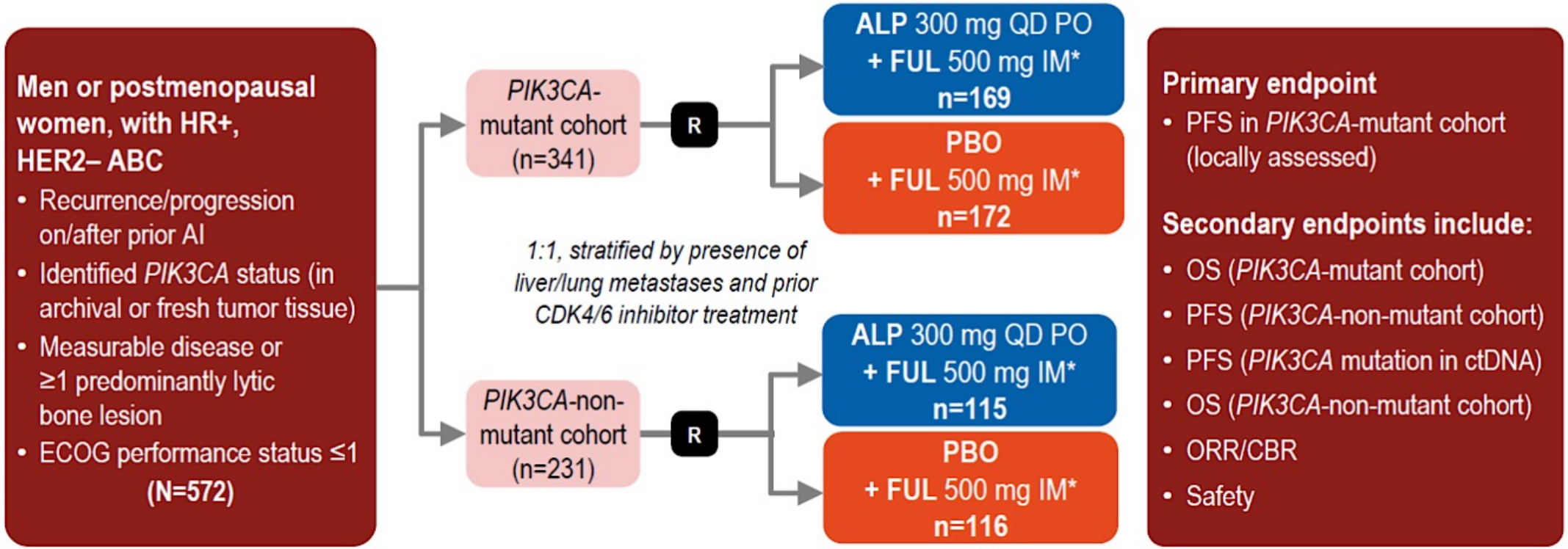


*Enrollment to Arm B stops at target enrollment (n= approximately 250). Further enrollment will be a 1:1 randomization between Arm A and Arm C until target enrollment to Arm C is met (n= approximately 180)

Note: ESR1 mutation status will be centrally determined in plasma by ctDNA assay from a blood draw at baseline.

HR+ *PIK3CA*-Mutated Disease
Alpelisib (BYL-719) Is More α-Specific

- **SOLAR-1 is a phase 3 randomized trial investigating the addition of alpelisib to fulvestrant in *PIK3CA*-mutated HR+/HER2– BC**



PIK3CA mutations were detected using an alternative tumour tissue-based companion diagnostic PCR test for 11 mutations, including the most common hotspots

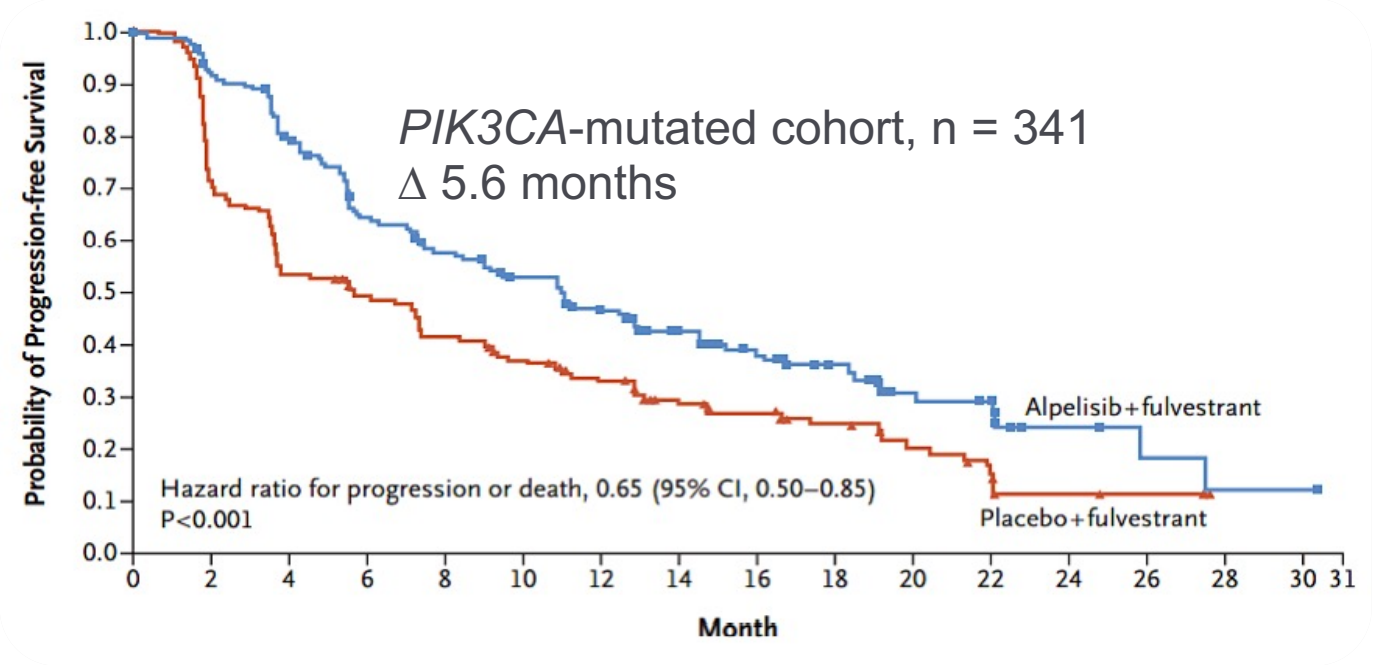
- ALP, alpelisib; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; CBR, clinical benefit rate; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant;
- IM, intramuscular; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily.

a. Clinicaltrials.gov. NCT02437318; b. André F, et al. N Engl J Med. 2019;380:1929-1940.

Option for Patients Whose Tumors Harbor *PIK3CA* Mutations
Fulvestrant + *Alpelisib*

SOLAR-1 (Phase 3): Fulvestrant ± Alpelisib

(Progression on or after AI)



- Numerical improvement in median OS of 7.9 months in the mutated cohort[b]
- Discontinuation rate was 25% in FUL + ALP arm vs 4.2% in the FUL arm[a]
- Most common side effects (grade 3): hyperglycemia (36%), rash (10%), and diarrhea (7%)[a]
- **6% had prior CDK4/6 inhibitor**

Median PFS[a]

- 11.0 months (ALP + FUL) vs 5.7 months (FUL)
- HR = 0.65 (95% CI: 0.50, 0.85); *P* < .001

ALP, alpelisib; FUL, fulvestrant.

a. Andre F, et al. N Engl J Med. 2019;380:1929-1940; b. Andre F, et al. Ann Oncol. 2021;32:208-217

Alpelisib + ET (Fulvestrant vs Letrozole) in *PIK3CA*-Mutated ABC *BYLieve*

- **BYLieve is a phase 2 trial assessing alpelisib + ET (fulvestrant or letrozole) in *PIK3CA*-mutated HR+/HER2− ABC in the post-CDK4/6i setting**

- Men or pre/postmenopausal women
- HR+/HER2− ABC with a *PIK3CA* mutation
- Last line of prior therapy: CDK4/6i + ET, systemic chemotherapy or ET
- ECOG PS ≤ 2
- Measurable disease (per RECIST v1.1) or ≥ 1 predominantly lytic bone lesion

Patients who received CDK4/6i + AI as immediate prior treatment (n = 112)
Cohort A

Alpelisib 300 mg QD + fulvestrant 500 mg

Patients who received CDK4/6i + fulvestrant as immediate prior treatment (n = 112)
Cohort B

Alpelisib 300 mg QD + letrozole 2.5 mg

Patients who progression on/after AI and receive chemotherapy as immediate prior treatment (n = 112)
Cohort C

Alpelisib 300 mg QD + fulvestrant 500 mg

Treatment crossover between cohorts not permitted

Primary endpoint

- Proportion of patients alive without PD at 6 months in each cohort

Secondary endpoints

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

DOR, duration of response; ET, endocrine therapy; PD, progressive disease.

Rugo HS, et al. J Clin Oncol. 2020;38(15_Suppl):1006.

Activity With PI3K Inhibitors and Various Endocrine Partners

- **PFS benefit in 2L metastatic setting after progression on CDK4/6i is ~ 5 to 7 months**

	BYLieve: PI3Ki + ET in HR+/HER2– BC With *PIK3CA* Mutation and PD on CDK4/6 Inhibition		
	Cohort A[a] (n = 121)	Cohort B[b] (n = 115)	Cohort C[c] (n = 115)
Cohort population	CDK4/6i + AI as immediate prior tx	CDK4/6i + fulvestrant as immediate prior tx	Chemo or ET as immediate prior tx
Endocrine partner	Fulvestrant	Letrozole	Fulvestrant
PI3Ki	Alpelisib	Alpelisib	Alpelisib
Median PFS, mo	7.3	5.7	5.6
HR (PI3Ki vs control)	NA	NA	NA

PD, progressive disease; tx, treatment.

a. Rugo HS, et al. Lancet Oncol. 2021;22:489-498; b. Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2020; December 8-11, 2020; Virtual. Presentation PD2-07; c. Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2021; December 7-10, 2021; San Antonio, TX. Presentation PD13-05.

Lessons Learned From SOLAR-1 and BYLieve Trials

	SOLAR-1[a] Fulvestrant + Alpelisib	BYLieve Cohort A[b] Fulvestrant + Alpelisib	BYLieve Cohort B[c] Letrozole + Alpelisib
Prior Rx in metastatic setting, %			
First line	52	70.1	52.4
Second line	47	16.5	44.4
Third line	-	1.6	1.6
Prior CDK4/6i, %	5.3	100	100
Median PFS, months	11.0	7.3	5.7
ORR, % (measurable disease)	36	21	18
CBR, % (measurable disease)	57	42	32
Decrease in best % change from baseline	75.9	70.1	66.3
Median relative dose intensity, %	82.7	89.9	87.6
AEs leading to discontinuation (≥ 1.5%), %	25	20.5	14.3
Hyperglycemia	6.3	1.6	0.8
Rash	3.2	3.9	3.2

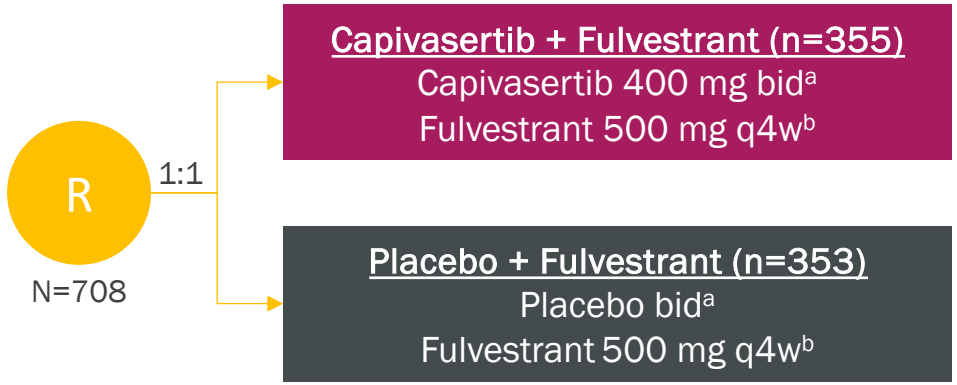
- AE, adverse event; CBR, clinical benefit rate; ORR, overall response rate.

a. André F, et al. N Engl J Med. 2019;380:1929-1940; b. Rugo H, et al. Presented at: 2020 ASCO Annual Meeting; May 29 to May 31, 2020; Virtual. Abstract 1006; c. Rugo H, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2020; December 8-11, 2020; Virtual. Presentation PD2-07.

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Study Design and Patients

Key Eligibility Criteria

- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6i allowed (at least 51% required)



Dual primary endpoints: PFS by investigator in overall and in AKT pathway-altered tumors[c]
Secondary endpoints: OS, ORR
Stratification Factors: Liver mets, prior CDK4/6i, region

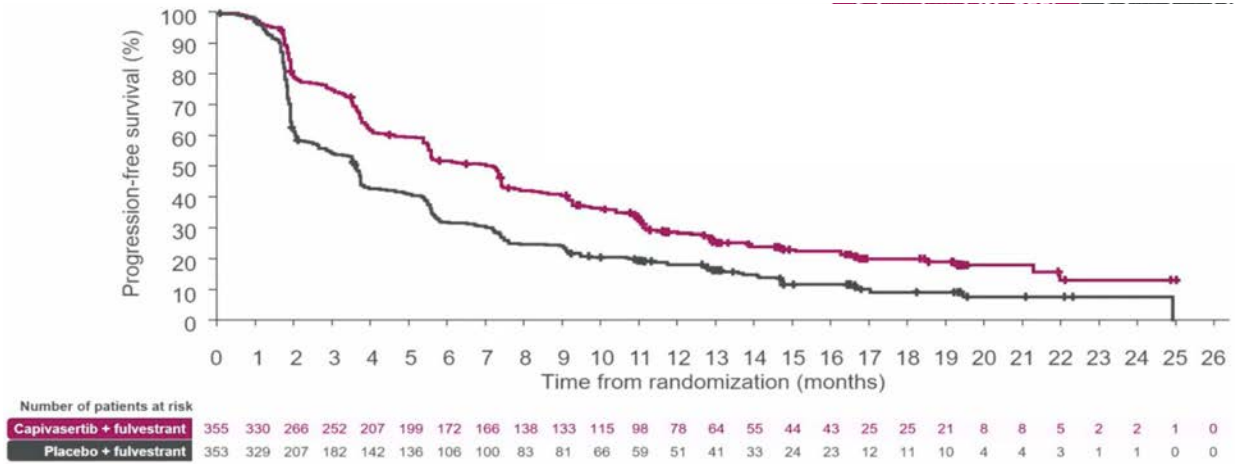
Patient Characteristics, n (%)		Overall Population		AKT Pathway Altered	
		C+F (n=355)	P+F (n=353)	C+F (n=155)	P+F (n=134)
Median age (range), years		59 (26-84)	58 (26-90)	58 (36-84)	60 (34-90)
Metastatic sites	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver[d]	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
HR status[e]	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
	ER+/PR–	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
	Unknown	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine resistance	Primary	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)
Prior endocrine therapy for ABC	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Prior CDK4/6i for ABC		**245 (69.0)**	**244 (69.1)**	**113 (72.9)**	**91 (67.9)**
Prior CT	(Neo)adjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)
AKT pathway alteration		155 (43.7)	134 (38.0)	-	-

[a] 4 days on, 3 days off. [b] Cycle 1, days 1 and 15; then q4w. [c] AKT pathway-altered tumors: ≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration. [d] Baseline stratification factor. [e] One patient in the C+F group was ER negative.

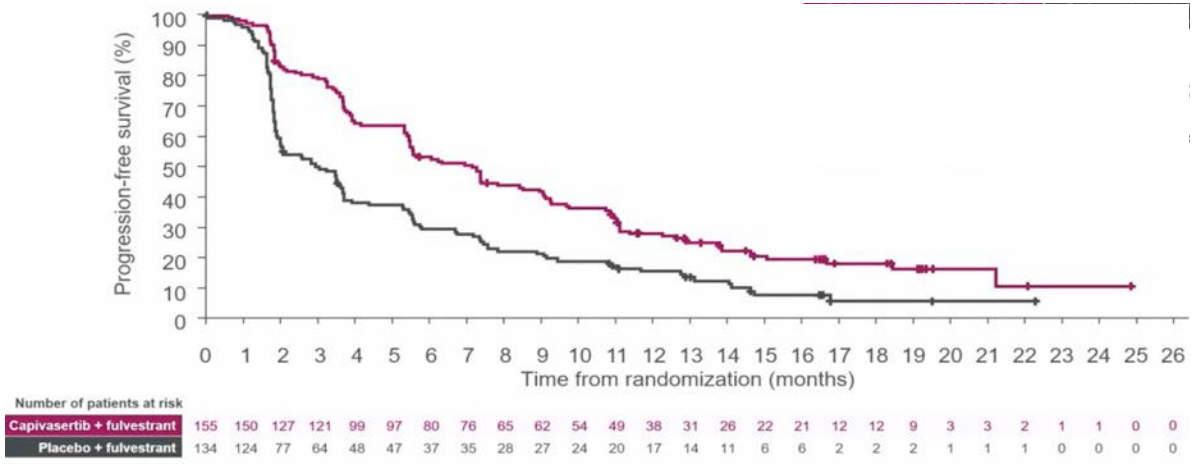
Turner NC, et al. SABCS 2022; Turner et al NEJM 2023

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: PFS

PFS by Investigator in Overall Population



PFS by Investigator in the AKT Pathway-Altered Population



Overall Population	C+F (n=355)	P+F (n=353)
PFS events	258	293
Median PFS, mo (95% CI)	7.2 (5.5-7.4)	3.6 (2.8-3.7)
Adjusted HR (95% CI)	0.60 (0.51-0.71)	
Two-sided *P* value	<0.001	

AKT Pathway-Altered Population	C+F (n=155)	P+F (n=134)
PFS events	121	115
Median PFS, mo (95% CI)	7.3 (5.5-9.0)	3.1 (2.0-3.7)
Adjusted HR (95% CI)	0.50 (0.38-0.65)	
Two-sided *P* value	<0.001	

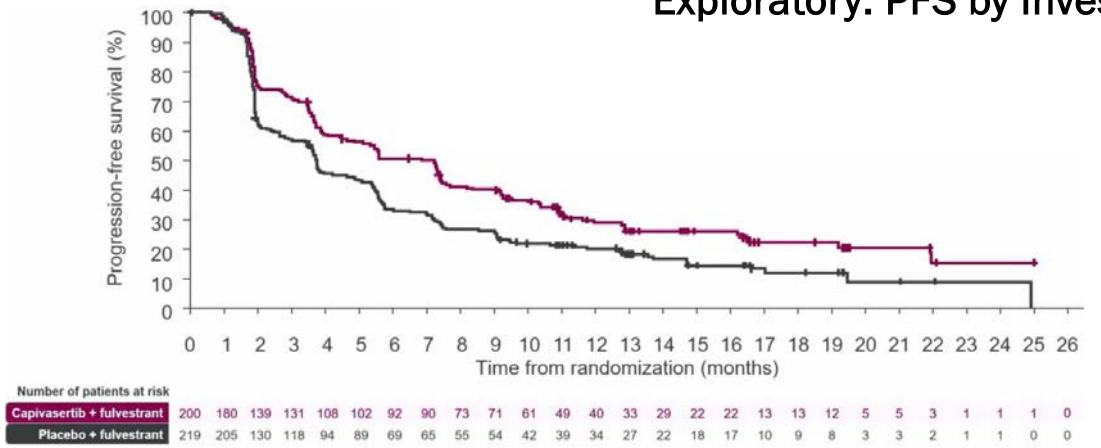
- PFS benefit was observed in all key subgroups, including regardless of prior use of CDK4/6i and liver metastases

HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6i, and geographic region.

Turner NC, et al. SABCS 2022. Abstract GS3-04; Turner et al NEJM 2023.

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: PFS (cont'd) and ORR

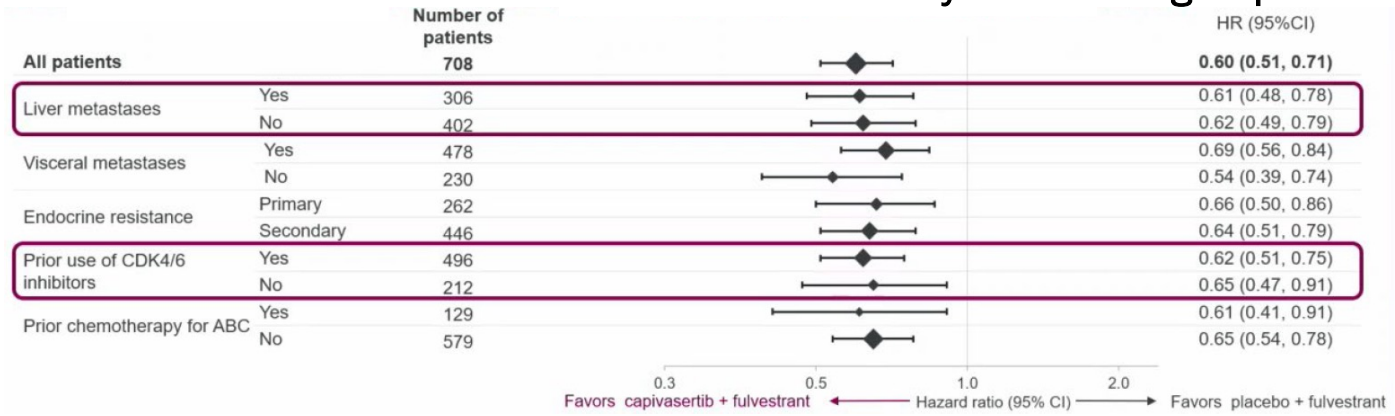
Exploratory: PFS by Investigator in the Nonaltered Population[1]



Nonaltered Population	C+F (n=200)	P+F (n=219)
PFS events	137	178
Median PFS, mo (95% CI)	7.2 (4.5-7.4)	3.7 (3.0-5.0)
Adjusted HR (95% CI)	0.70 (0.56-0.88)	

- The nonaltered population included:
  - AKT pathway alteration **not detected**: C+F arm: 142/355 (40.0%), P+F arm: 171/353 (48.4%)
  - **Unknown**: C+F arm: 58/355 (16.3%), P+F arm: 48/353 (13.6%)

INV-Assessed PFS by Select Subgroups in the Overall Population[1,2]



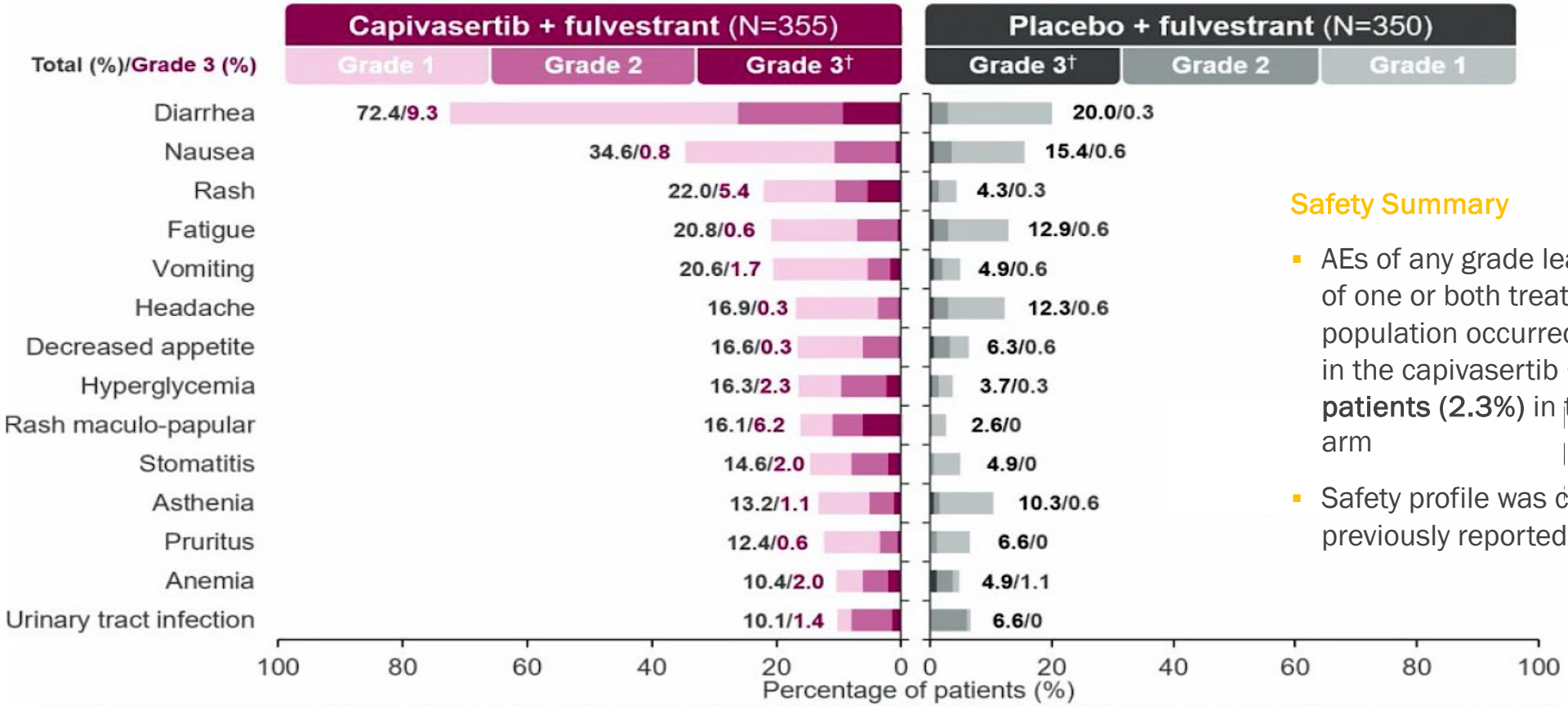
mPFS (95% CI), mo		C+F	P+F
Prior CDK4/6i	Yes (n=496)	5.5 (3.9-6.8)	2.6 (2.0-3.5)
	No (n=212)	10.9 (7.4-13.0)	7.2 (4.8-7.9)
Prior CT for MBC	Yes (n=129)	3.8 (3.0-7.3)	2.1 (1.9-3.6)
	No (n=579)	7.3 (5.6-8.2)	3.7 (3.4-5.1)
Liver metastases	Yes (n=306)	3.8 (3.5-5.5)	1.9 (1.8-1.9)
	No (n=402)	9.2 (7.4-11.1)	5.5 (3.9-5.8)

HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6i.

1. Turner NC, et al. SABCS 2022. Abstract GS3-04. 2. Oliveira M, et al. ESMO Breast 2023. Abstract 187O; Turner et al NEJM 2023

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Safety

AEs (>10% of Patients) in Overall Population



Safety Summary

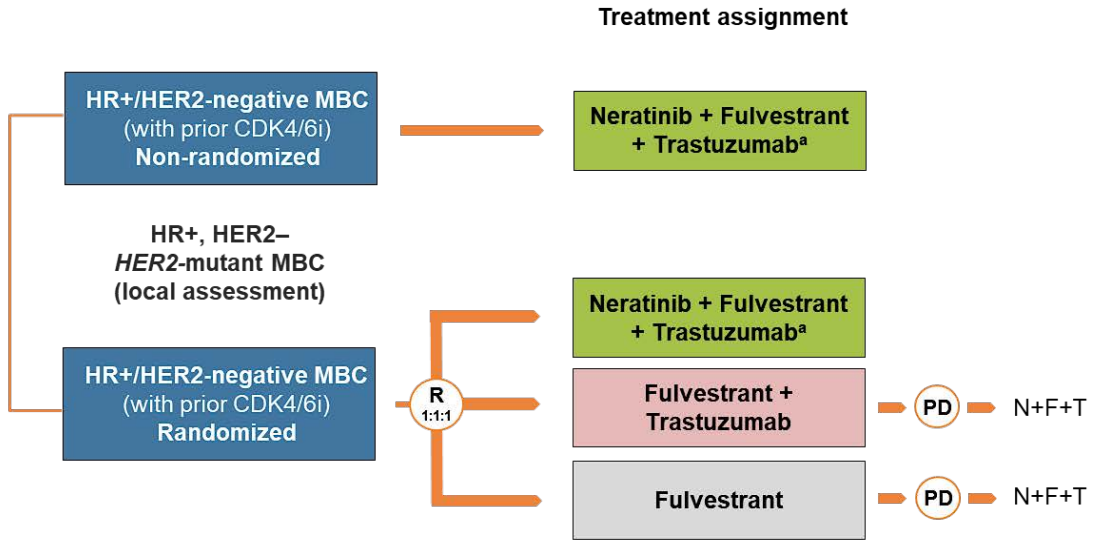
- AEs of any grade leading to discontinuation of one or both treatments in the safety population occurred in **46 patients (13.0%)** in the capivasertib + fulvestrant arm and **8 patients (2.3%)** in the placebo + fulvestrant arm
- Safety profile was consistent with that previously reported

Turner NC, et al. SABCS 2022. Abstract GS3-04; Turner et al NEJM 2023

HER2 Mutation: Combinations needed for improved efficacy and durability

SUMMIT (NCT01953926): ER+ HER2- *ERBB2* mut Cohort

***HER2* mutation: 8% ER+ MBC**
15%: met ILC



[a]Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

***HER2*-mutant MBC**

Primary endpoint

- Confirmed objective response rate (ORR; RECIST v1.1, centrally assessed)

Secondary endpoints

- Confirmed ORR (investigator-assessed)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety and PROs

Treatment Regimen	ORR	PFS (months)	DOR (months)
Neratinib (n=23)	17%	3.6	6.5
Neratinib + Fulvestrant (n=47)	**30%**	**5.4**	**9.2**
Neratinib + Fulvestrant +Trastuzumab (n=51)	**35.3%**	**8.2**	**14.3**

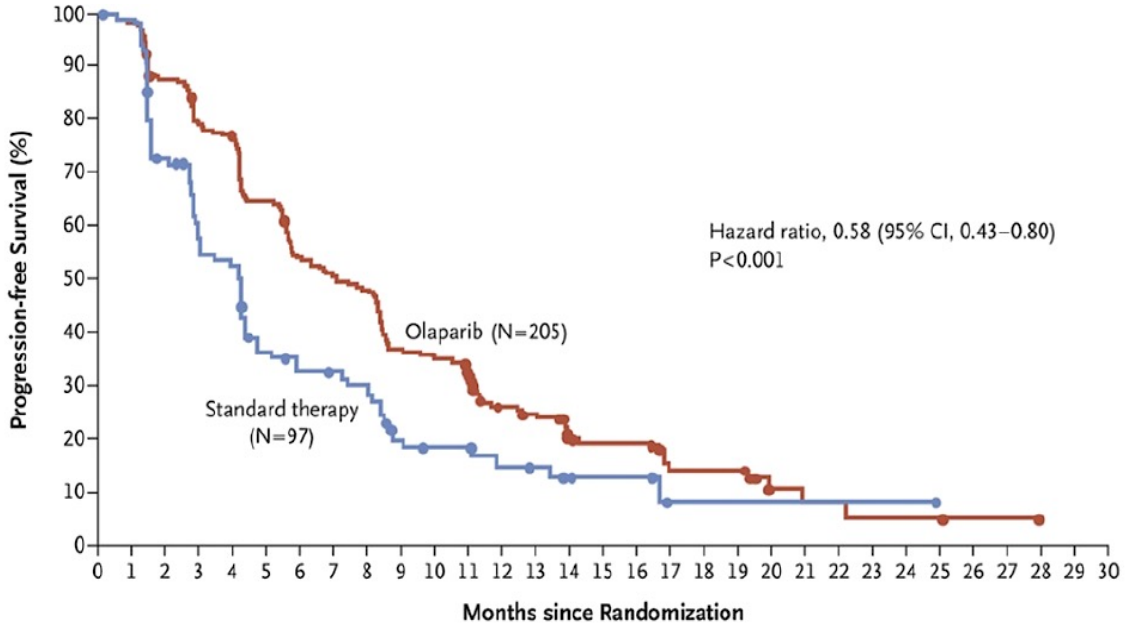
Addition of T to N prolongs suppression of HER3 phosphorylation in HR+, HER2-negative, *HER2*-mutant breast cancer cell line model

- Tucatinib + Trastuzumab Basket Study (NCT04579380)
- BDTX0819 Potent and Selective Inhibitor of the Allosteric Oncogenic ErbB Family (NCT04209465)
- Trastuzumab Deruxtecan: DESTINY-pantumor01 (NCT04639219)

Jhaveri et al SABCS 2021; Jhaveri et al ASCO 2022; Jhaveri et al Ann of Oncol 2023

PARP Inhibitors US FDA Approved for g*BRCA* mutant MBC

Olaparib
Phase 3 OlympiAD



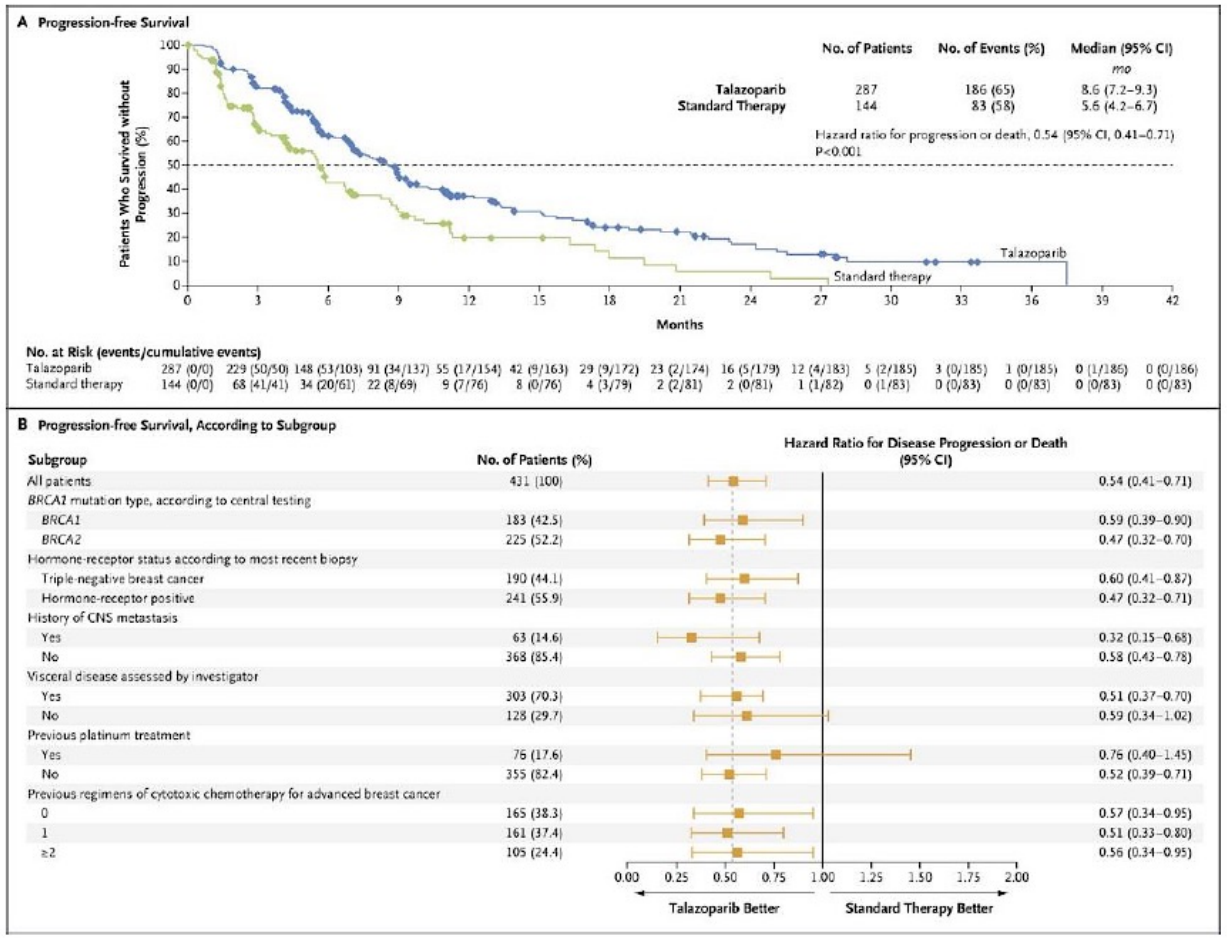
No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

Improvement in PFS with PARPi compared with chemotherapy

Benefit regardless of subgroup

Talazoparib
Phase 3 EMBRACA



Robson et al NEJM 2017; Litton et al NEJM 2018

European Journal of Cancer 184 (2023) 39–47

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

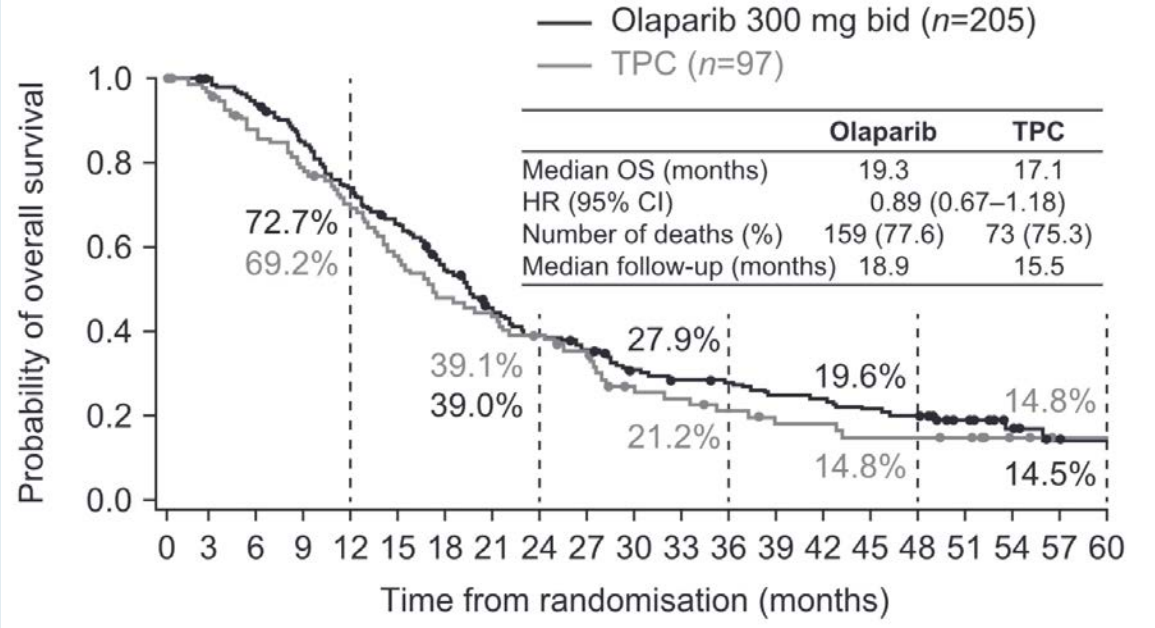
Original Research

OlympiAD extended follow-up for overall survival and safety: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer

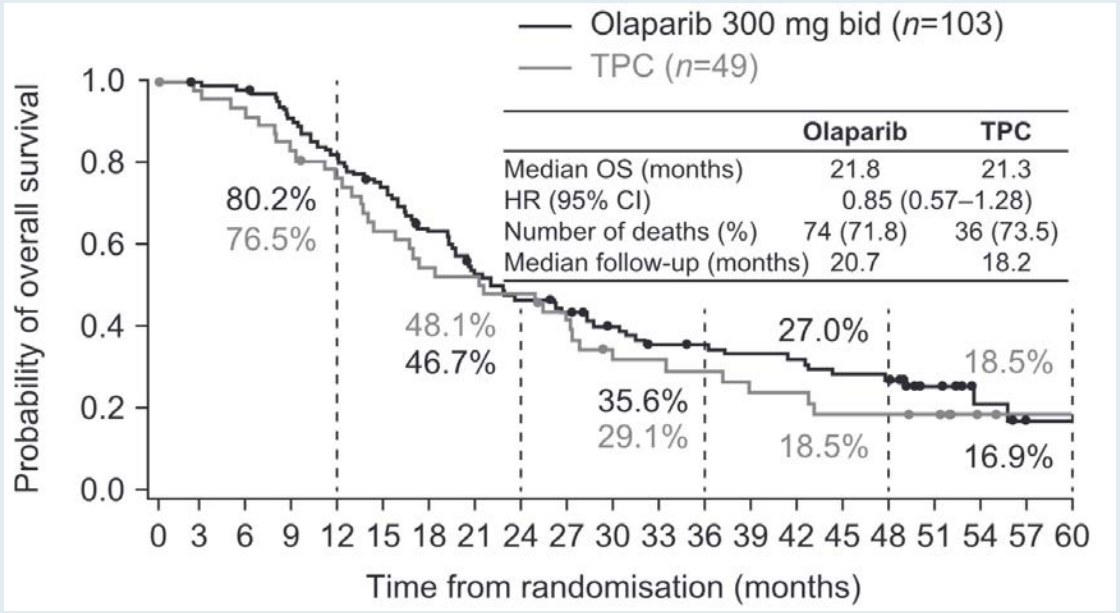
Mark E. Robson [a,*], Seock-Ah Im [b], Elzbieta Senkus [c], Binghe Xu [d], Susan M. Domchek [e], Norikazu Masuda [f], Suzette Delaloge [g], Nadine Tung [h], Anne Armstrong [i], Mike Dymond [j], Anitra Fielding [k], Allison Allen [k,**], Pierfranco Conte [l,m]

OlympiAD: Extended Follow-Up for Overall Survival

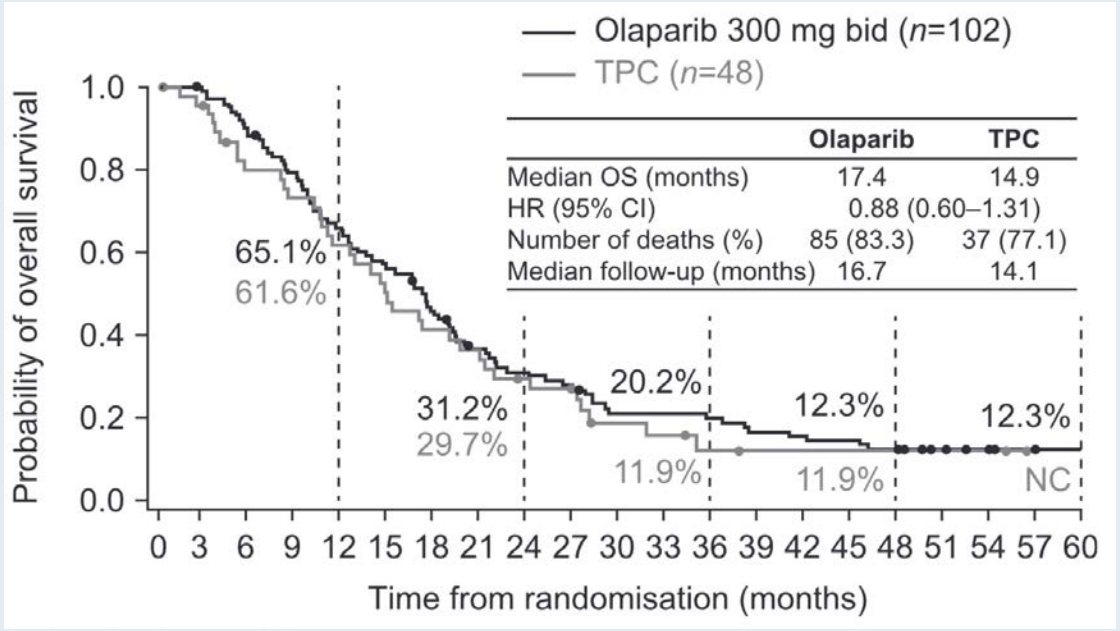
Overall population



HR-positive



TNBC



Robson ME et al. *Eur J Cancer* 2023;184:39-47.

RTP RESEARCH TO PRACTICE

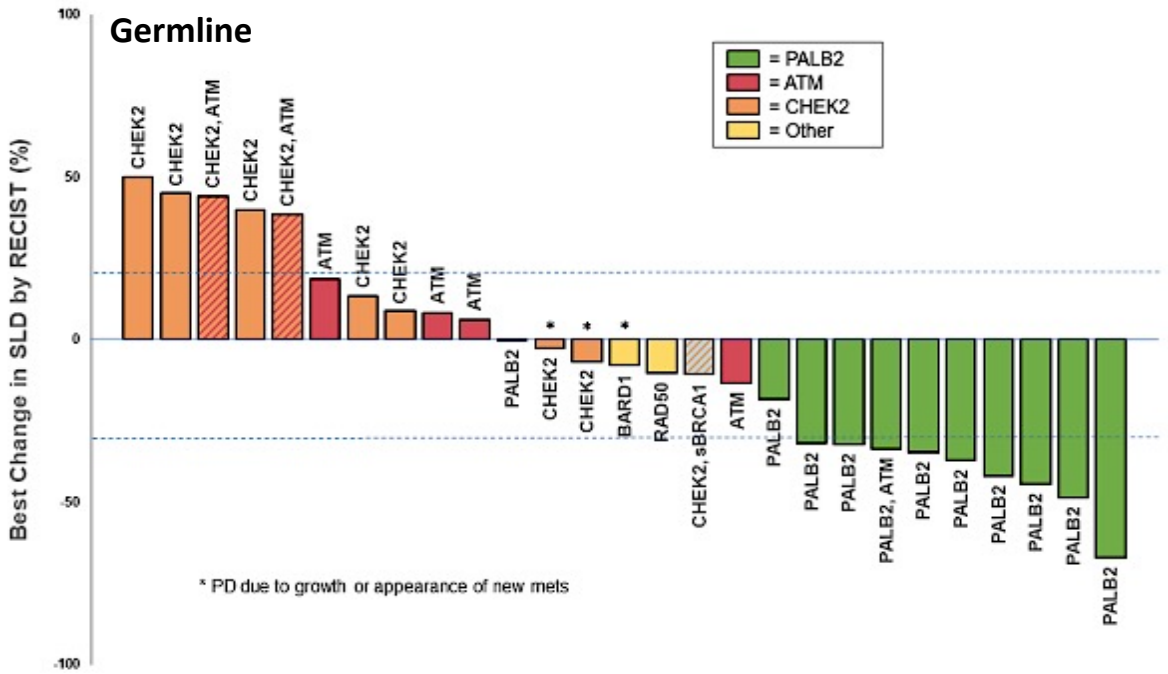
TBCRC 048: A Phase 2 Study of Olaparib in MBC With Germline or Somatic Mutations in Homologous Recombination Pathway Genes

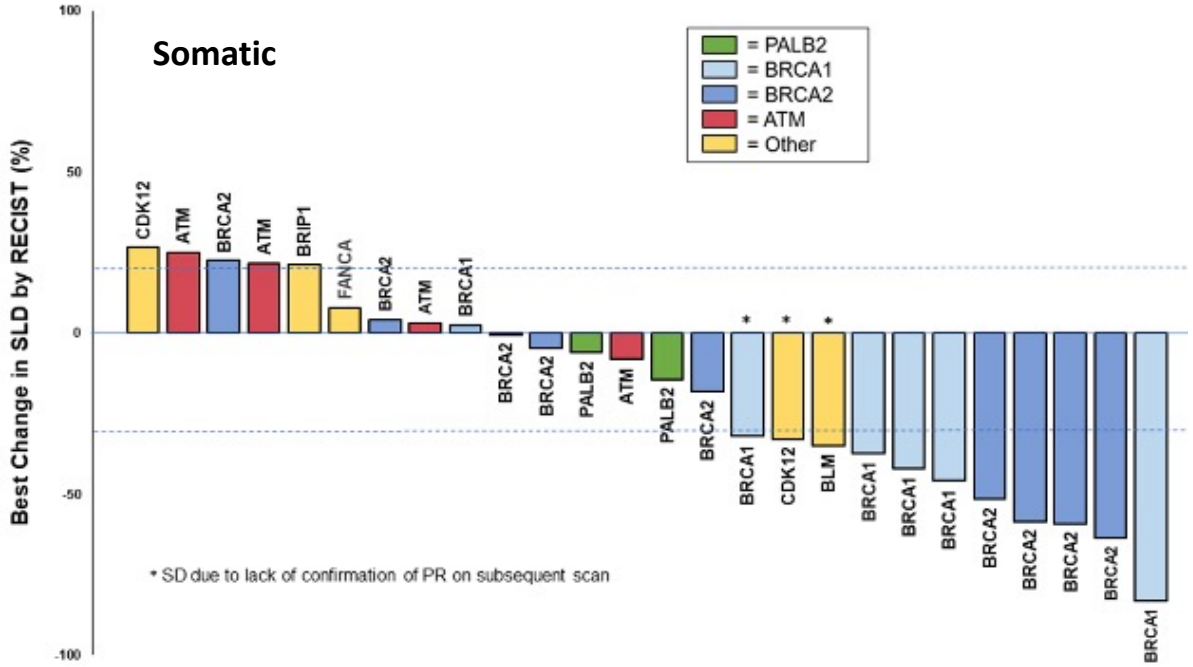
Germline (Cohort 1)		Somatic (Cohort 2)[4]	
• *CHEK2*[1,2]	n=8	• *sBRCA1*[5]	n=6
• *ATM*	n=4	• *sBRCA2*	n=9
• *ATM & CHEK2*[1]	n=2	• *ATM*[6]	n=4
• *PALB2*[3]	n=11	• *PAL2*	n=2
• *BARD1*	n=1	• *CDK12*	n=2
• *RAD50*	n=1	• *BRIP1*	n=1
		• *BLM*	n=1
		• *FANCA*	n=1

14 *ATM CHEK2*

15 *sBRCA1/2*

PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr Somatic: 0/2 – both SD* (limited assessments)	8/16 PR (50%)	0/13 germline 0/4 somatic



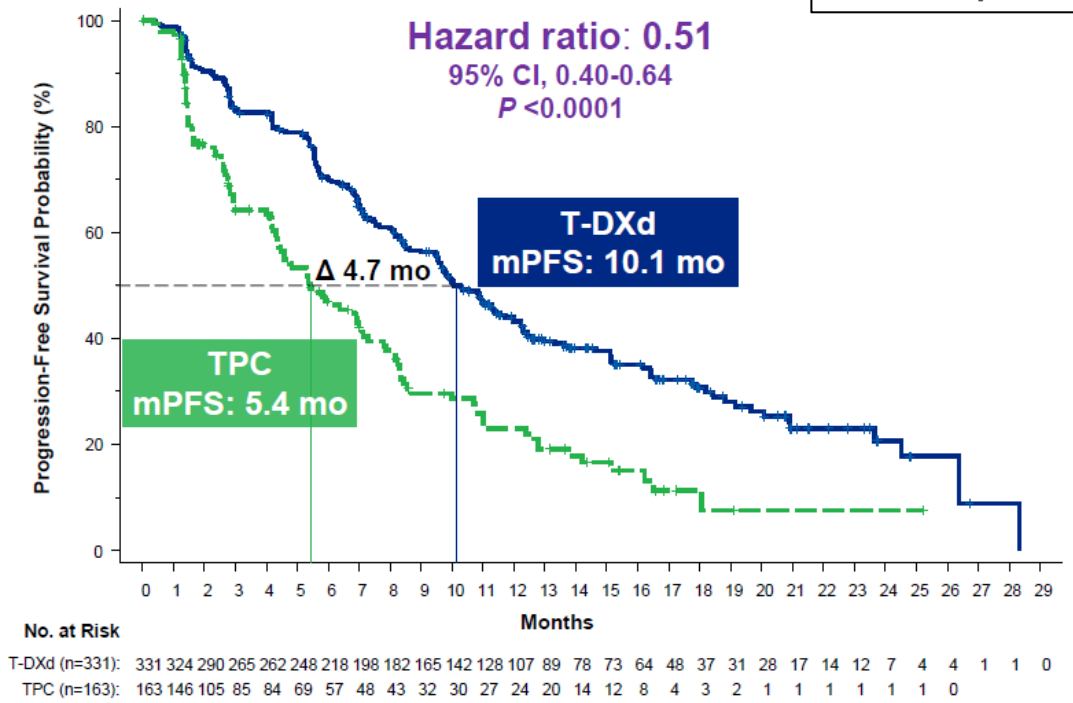


Tung NM, et al. *J Clin Oncol*. 2020;38:4274-4282

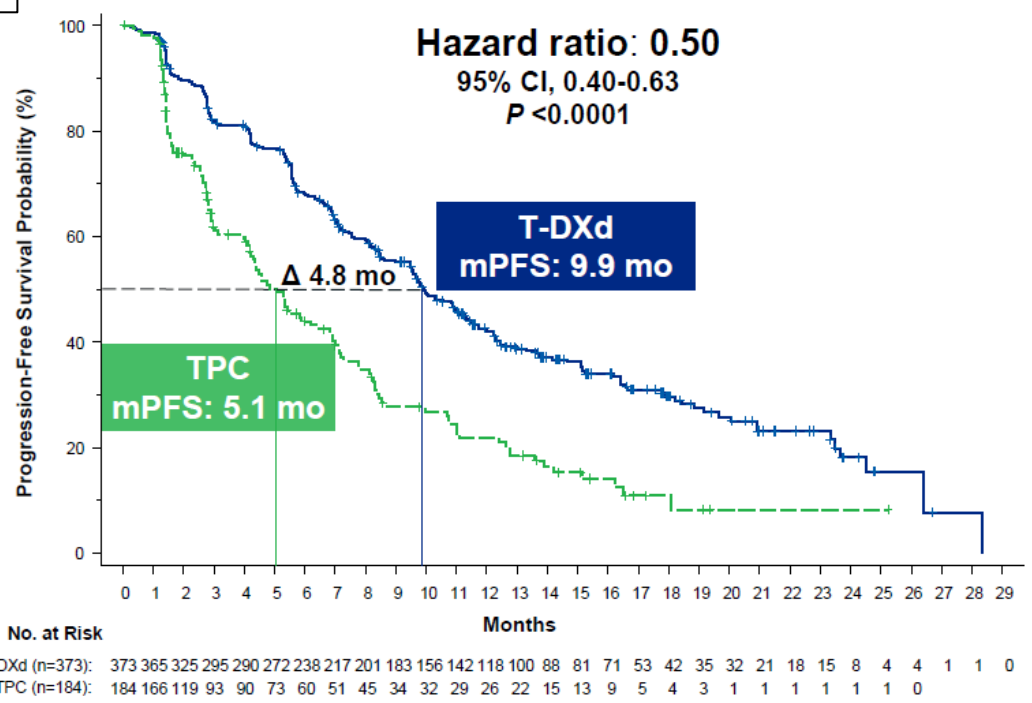
Trastuzumab Deruxtecan in HER2-Low Metastatic BC
DESTINY-Breast04 Phase 3: PFS

70% prior CDK4/6 inhibitors
Median 1 prior chemo

PFS in HR+



PFS in All Patients

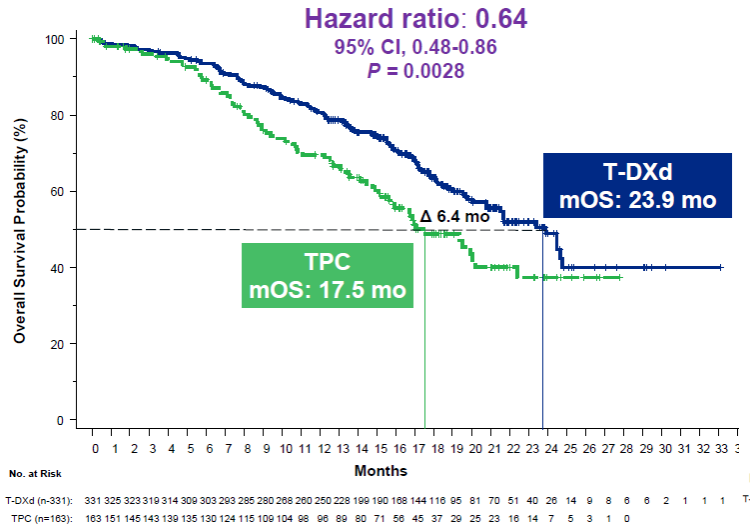


PFS	HR+		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median PFS, months	10.1	5.4	9.9	5.1
HR (95% CI); *P* value	0.51 (0.40, 0.64); < .001		0.50 (0.40, 0.63); < .0001	

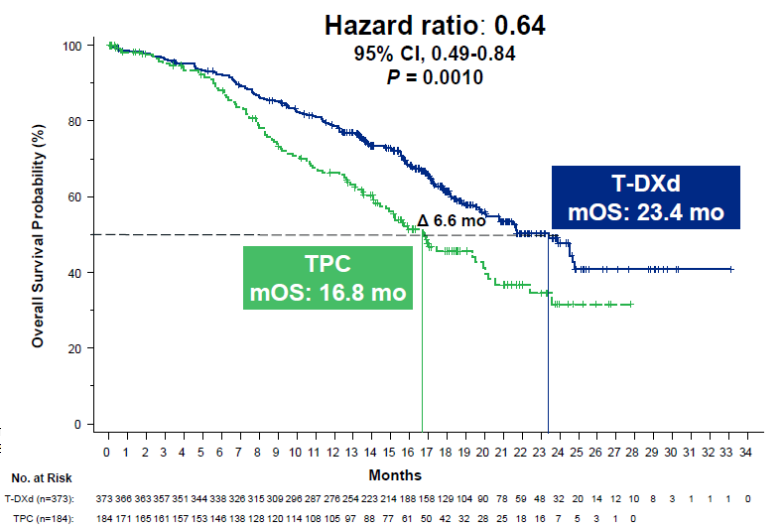
T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Trastuzumab Deruxtecan in HER2-Low Metastatic BC
DESTINY-Breast04 Phase 3: OS

OS in HR+



OS in All Patients



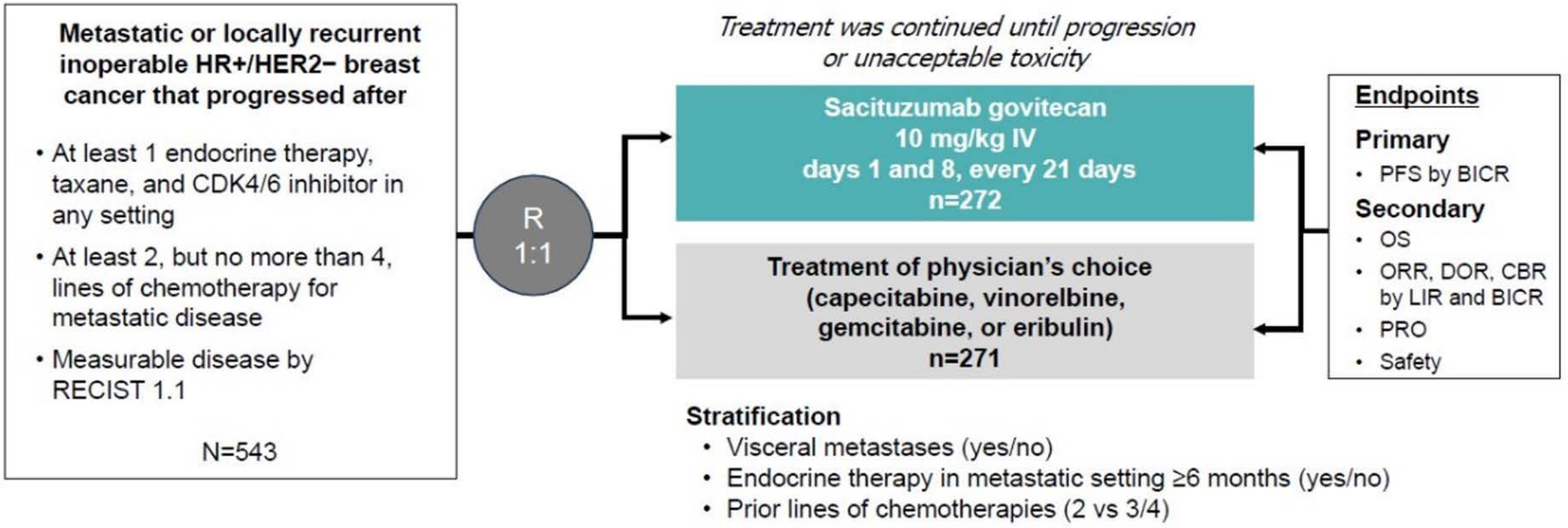
Response	HR+		HR-	
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Confirmed ORR, %	52.6	16.3	50.0	16.7
CR	3.6	0.6	2.5	5.6
PR	49.2	15.7	47.5	11.1
PD	7.8	21.1	12.5	33.3
NE	4.2	12.7	7.5	5.6
CBR, %	71.2	34.3	62.5	27.8
Median DOR, months	10.7	6.8	8.6	4.9

OS	HR+		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median OS, months	23.9	17.5	23.4	16.8
HR (95% CI); *P* value	0.64 (0.48, 0.86); .0028		0.64 (0.49, 0.84); .0010	

CR, complete response; DOR, duration of response; NE, not evaluable; PD, progressive disease; PR, partial response.

Modi S, et al. Presented at: 2020 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL. Abstract LBA3; Modi S, et al. N Engl J Med. 2022;387:9-20

Sacituzumab Govitecan vs TPC in HR+/HER2− mBC
TROPiCS-02



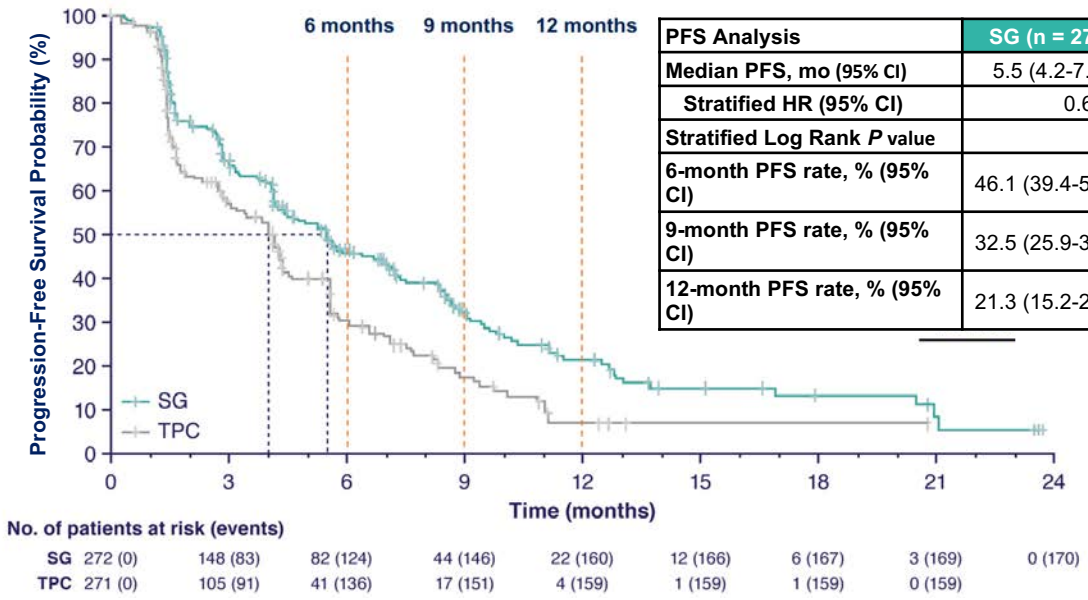
HR, hormone receptor; LIR, local investigator review; PRO, patient-reported outcomes.

Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS5-11

Sacituzumab Govitecan in HR+/HER2− Advanced BC
TROPiCS-02 Phase 3: Efficacy

BICR-Assessed PFS in the ITT Population

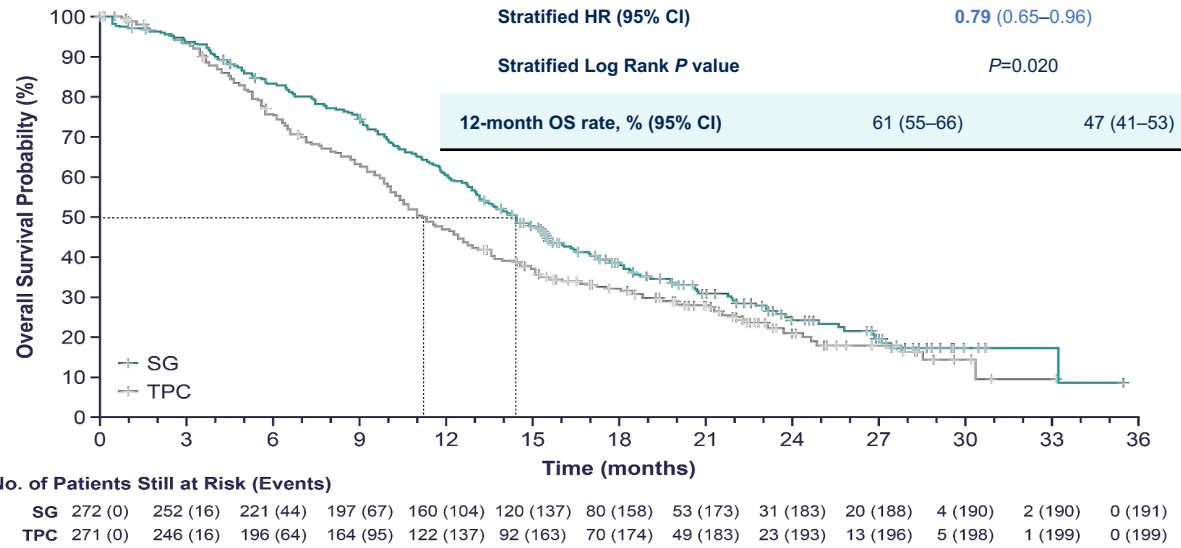
98% prior CDK4/6 inhibitors
Median 3 prior chemo



PFS Analysis	SG (n = 272)	TPC (n = 271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	0.66 (0.53-0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)

OS in the ITT Population (Second Interim Analysis)

	SG (n = 272)	TPC (n = 271)
Number of events	191	199
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	
12-month OS rate, % (95% CI)	61 (55–66)	47 (41–53)



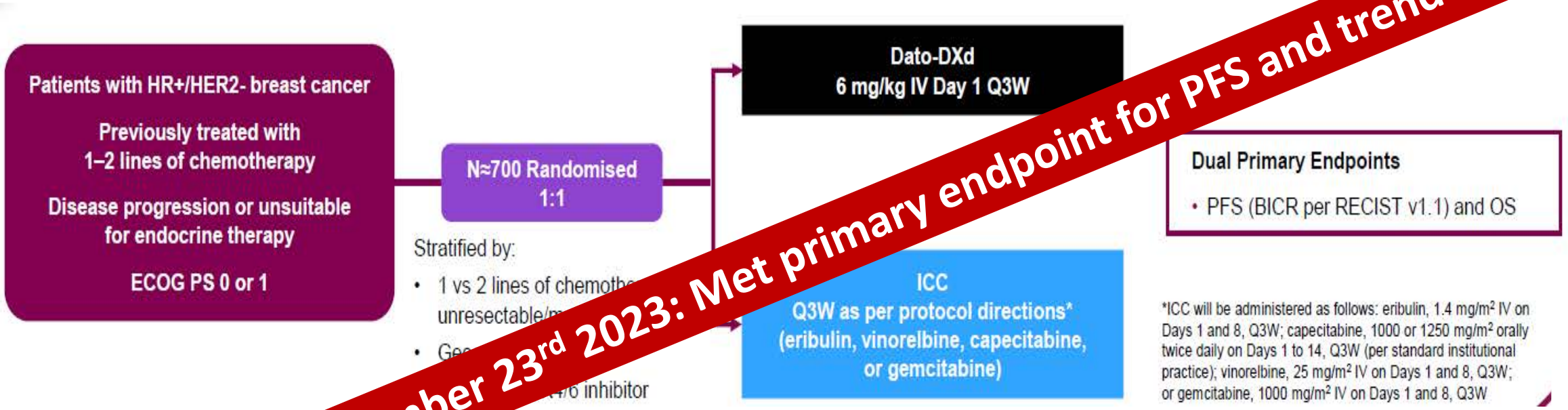
BICR, blinded independent central review; ITT, intention to treat; SG, sacituzumab govitecan.

- SG resulted in a 34% reduction in the risk of PD/death
- SG showed statistically significant improvement in OS vs TPC with 21% reduction in the risk of death
- Patients who received SG survived a median of ***3.2 months longer*** than those who received TPC
- SG resulted in PFS benefit consistent across all subgroup analysis, including patients with
  - ≥ 3 prior chemotherapy regimens in the metastatic setting
  - Visceral metastases
  - Endocrine therapy for MBC ≥ 6 months

Rugo H, et al. Presented at: 2020 ASCO Annual Meeting; May 29 to May 31, 2020; Virtual. Abstract LBA1001; Rugo et al The Lancet 2023

TROPION-01: Datopotamab Deruxtecan for HR+/HER2- MBC: Study Design

Datopotamab Deruxtecan: Anti-trop-2 IgG1 Ab, cleavable tetrapeptide linker, DXd payload, DAR: 4

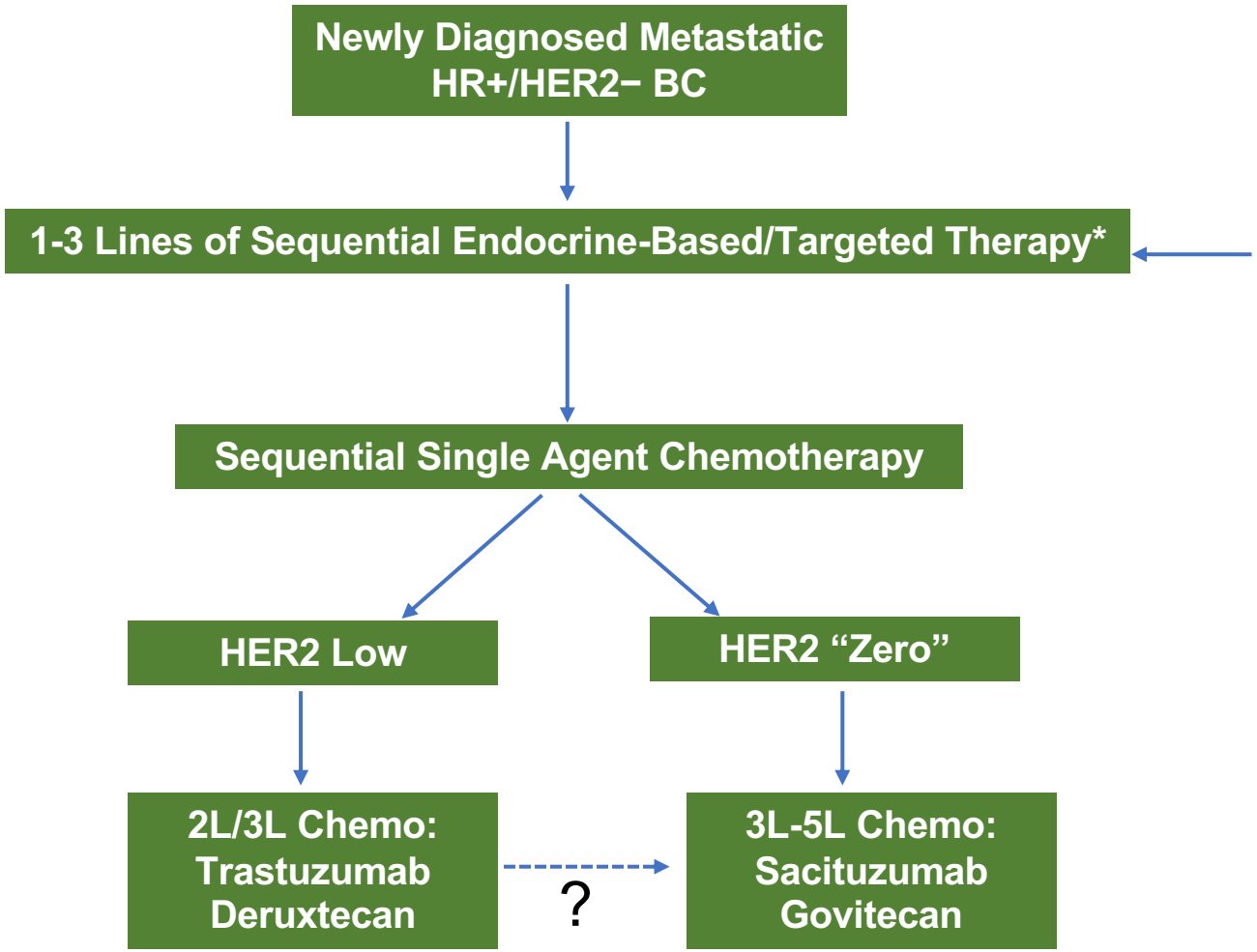


Press release September 23rd 2023: Met primary endpoint for PFS and trend seen for OS

antumor-01: ORR 27%; n=41

Bardia et al: Poster 274TiP ESMO 2022; Meric-Bernstam et al SABCS 2022

Treatment Roadmap for HR+/HER2− MBC Today in Clinic



1L: - AI/SERD + CDK4/6i

2L or 3L:
- SERD + PI3Ki (*PIK3CA* mutant)
- Oral SERD (*ESR1* mutation)
- ET + mTORi
- ET + AKTi?
- SERD + CDK4/6i
- ET

1L-3L: - *gBRCA1/2+*: *PARPi*

≥ 2L:
- Larotrectinib/Entrectinib (*NTRK* fusion)
- Pembrolizumab (MSI-H/dMMR, high TMB)
- Selpercatinib (RET alterations)

*Chemotherapy for visceral crisis.

Clinical Questions and Cases

Case Presentation: 66-year-old man with multiregimen-recurrent ER/PR-positive, HER2-negative metastatic breast cancer s/p ET/CDK is now receiving alpelisib; PIK3CA+, ATM copy loss

Dr Sunil Gandhi (Lecanto, Florida; 4-28-2021)

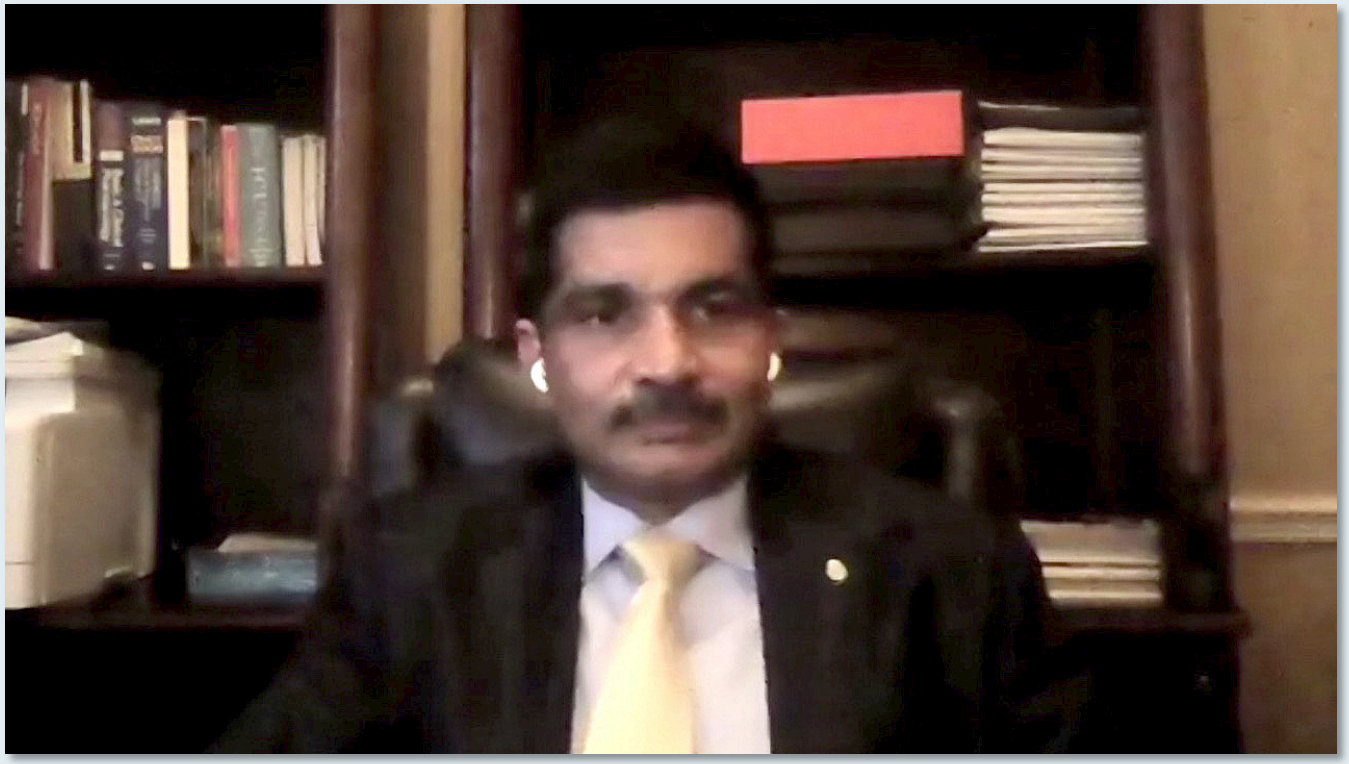
RTP RESEARCH TO PRACTICE

Case Presentation: 60-year-old woman with multiregimen-recurrent ER/PR-positive, HER2-negative metastatic breast cancer receives alpelisib; PIK3CA mutation

Dr Maen Hussein (The Villages, Florida; 9-28-2020)

RTP RESEARCH TO PRACTICE

Case Presentation: 55-year-old woman with ER-positive, HER2-negative recurrent metastatic breast cancer receives abemaciclib/anastrozole; ESR1 mutation



Dr Uday Dandamudi (New Port Richey, Florida; 10-19-2020)

RTP RESEARCH TO PRACTICE

Hormone Receptor-Positive Breast Cancer
Post-CDK4/6 Inhibitor Endocrine Treatment

- **Biomarker evaluation**
- **Oral SERDs**
  - **Elacestrant**
  - **Novel oral SERDs under investigation (camizestrant, imlunestrant)**
- **PI3K/AKT pathway inhibitors**
  - **Alpelisib**
  - **Capivasertib**

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TO PRACTICE

Discussion Question

For patients who experience disease progression on a CDK4/6 inhibitor with endocrine therapy for ER-positive metastatic breast cancer, testing is indicated for which alterations?

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TO PRACTICE

Discussion Question

A patient who has been receiving a CDK4/6 inhibitor with letrozole for ER-positive, HER2-negative metastatic breast cancer experiences disease progression after 18 months. Biomarker evaluation reveals a PIK3CA mutation and an ESR1 mutation. Regulatory and reimbursement issues aside which systemic treatment would you most likely recommend?

Case Presentation: 53-year-old woman experiences dramatic response to fulvestrant and abemaciclib for multiregimen-recurrent ER/PR-positive, HER2-low, PIK3CA-mutated metastatic breast cancer

Dr KS Kumar (Trinity, Florida; 10-17-2022)

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RESEARCH
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Hormone Receptor-Positive Breast Cancer
Antibody-Drug Conjugates

- **T-DXd in HER2-low, HR-positive disease**
  - **Efficacy and sequencing**
  - **Tolerability (ILD prevention and management, cardiac monitoring)**
- **Dato-DXd TROPION-Breast01 trial (press release and upcoming ESMO presentation)**

Discussion Question

Regulatory and reimbursement issues aside, would you likely offer trastuzumab deruxtecan at some point in the treatment course to a patient with ER-positive metastatic breast cancer with a HER2 mutation but an IHC score of 0?

How would you generally sequence trastuzumab deruxtecan and sacituzumab govitecan for a patient with ER-positive, HER2-low metastatic breast cancer who is eligible to receive both?

Discussion Question

Which of the following adverse events is most frequently observed with datopotamab deruxtecan?

Current Approaches and Future Strategies in Oncology: A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists and Research Institute

A CME/MOC- and NCPD-Accredited Event

Saturday, October 7, 2023
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — ER-Positive Breast Cancer: *Drs Burstein and Jhaveri*

Module 2 — Prostate Cancer: *Drs Morgans and Smith*

Module 3 — Non-Small Cell Lung Cancer: *Drs Riely and Wakelee*

Module 4 — Colorectal and Gastroesophageal Cancers:
Drs Bekaii-Saab and Philip

Module 5 — Chronic Lymphocytic Leukemia: *Drs Chanan-Khan and Kahl*

Prostate Cancer Faculty

Alicia K Morgans, MD, MPH
Associate Professor of Medicine
Harvard Medical School
Medical Director, Survivorship Program
Dana-Farber Cancer Institute
Boston, Massachusetts

Matthew R Smith, MD, PhD
Claire and John Bertucci Endowed Chair
in Genitourinary Cancers
Professor of Medicine
Harvard Medical School
Director, Genitourinary Malignancies Program
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

RTP
RESEARCH
TO PRACTICE

Role of Hormonal Therapy in Prostate Cancer (PC) Management

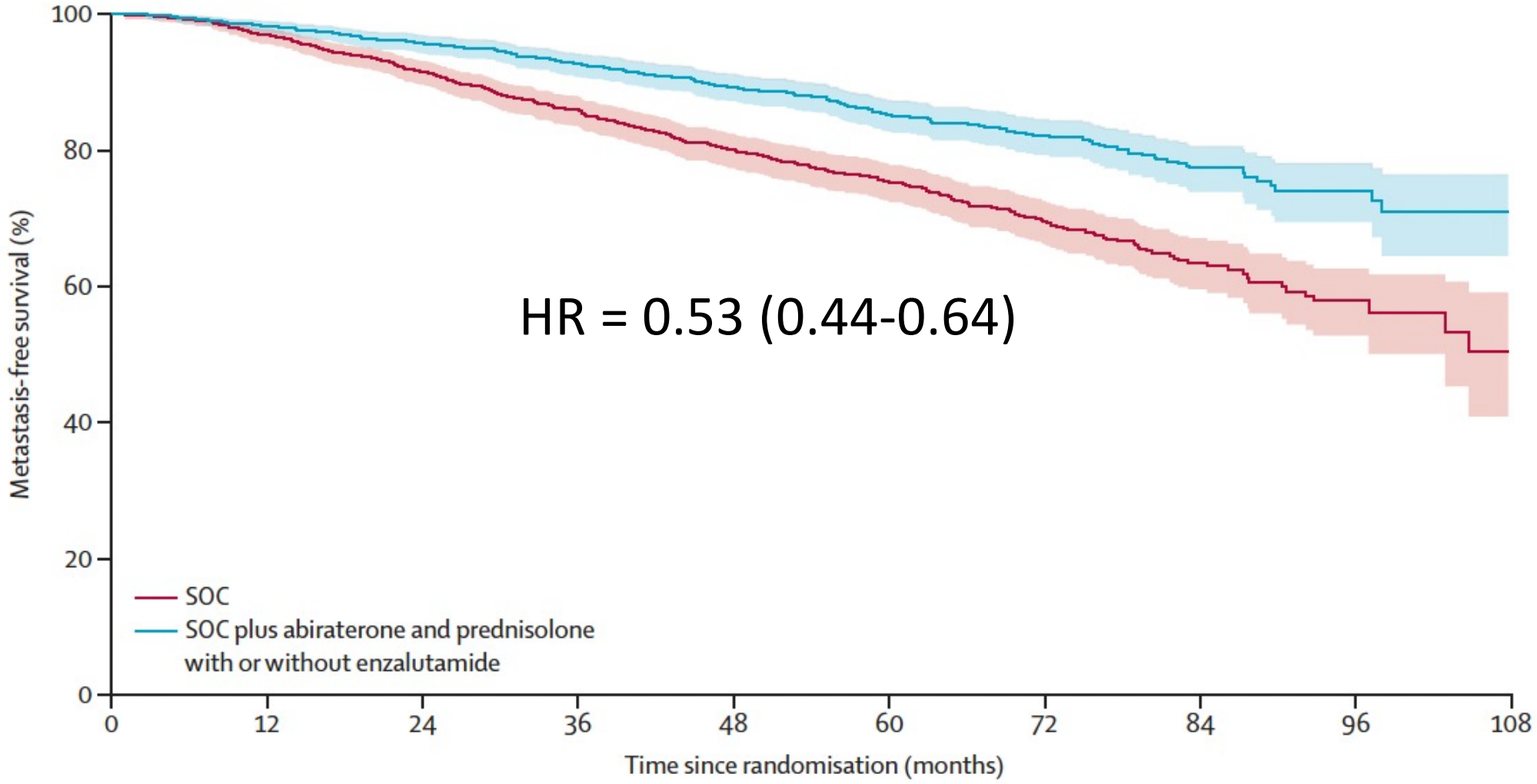
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

HARVARD MEDICAL SCHOOL

Matthew R. Smith, M.D.,Ph.D.
Professor of Medicine, Harvard Medical School
Director, MGH Genitourinary Malignancies Program

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

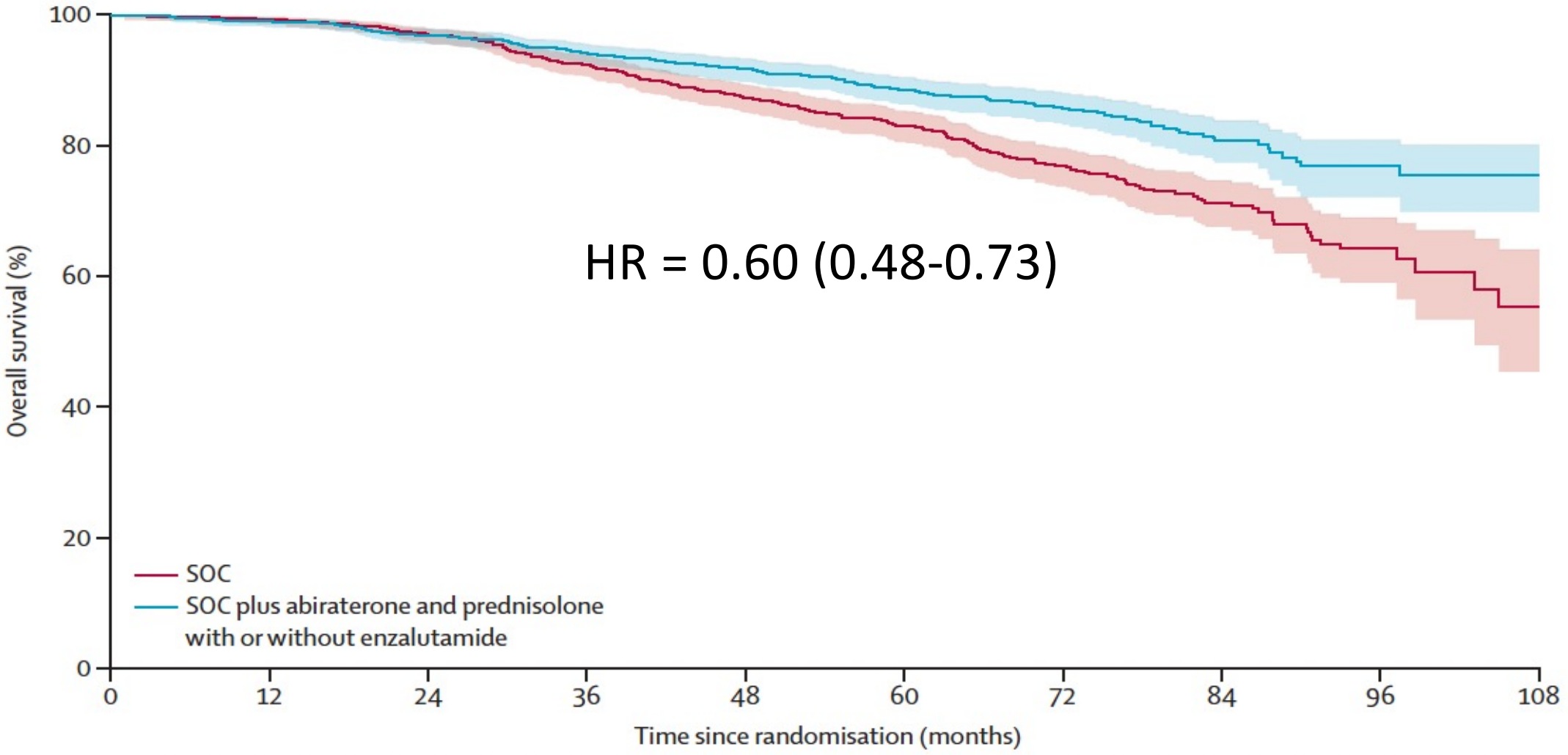
STAMPEDE: Abiraterone Acetate for High-Risk Non-Metastatic Castration-Sensitive Prostate Cancer



Attard *et al Lancet* 2022; 399: 447-460

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

STAMPEDE: Abiraterone Acetate for High-Risk Non-Metastatic Castration-Sensitive Prostate Cancer



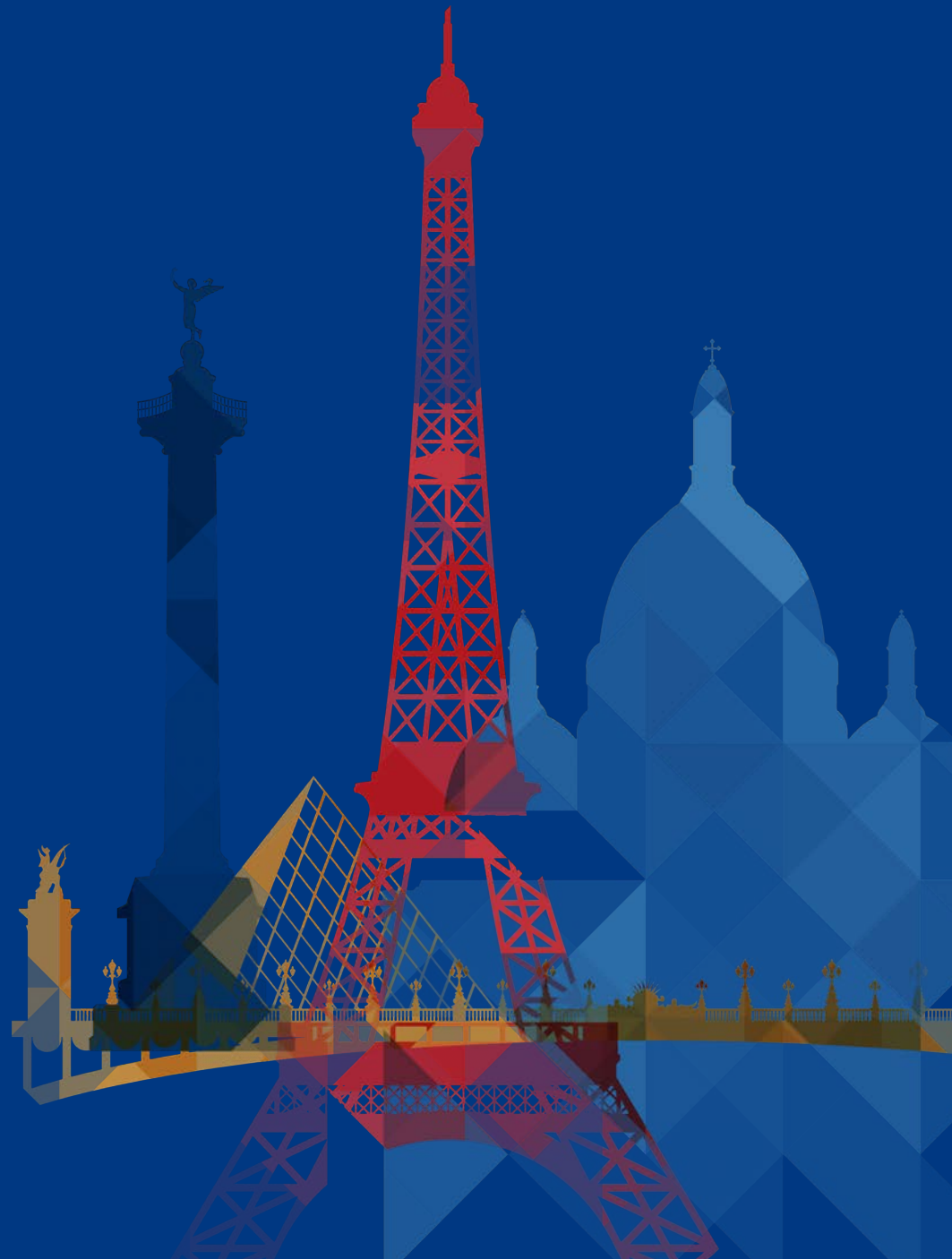
Attard *et al Lancet* 2022; 399: 447-460

PARIS 2022 ESMO congress

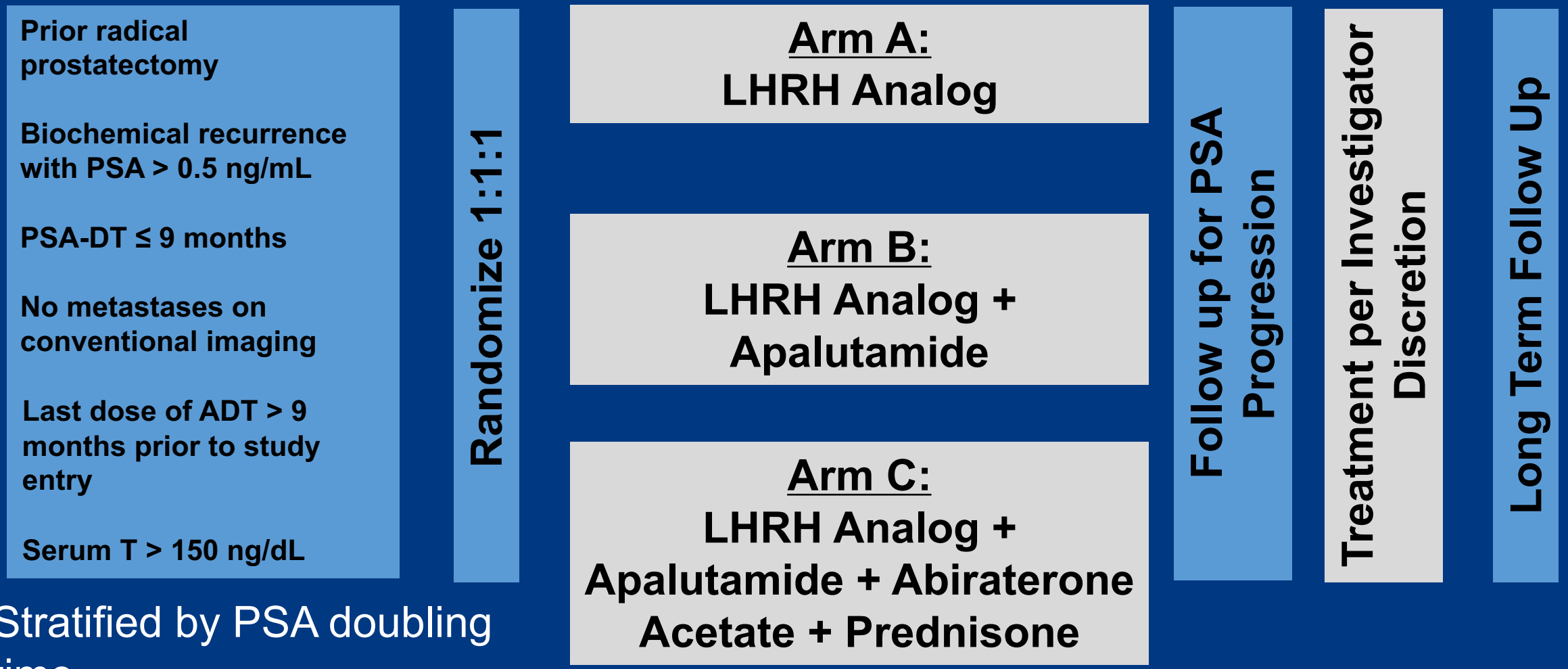
PRESTO: A Phase 3 Open-Label Study of Androgen Annihilation in Patients with High-Risk Biochemically Relapsed Prostate Cancer (AFT-19)

Rahul Aggarwal, on behalf of the Alliance AFT-19 Study Investigators

Paris, France
11 SEP 2022



Study Schema

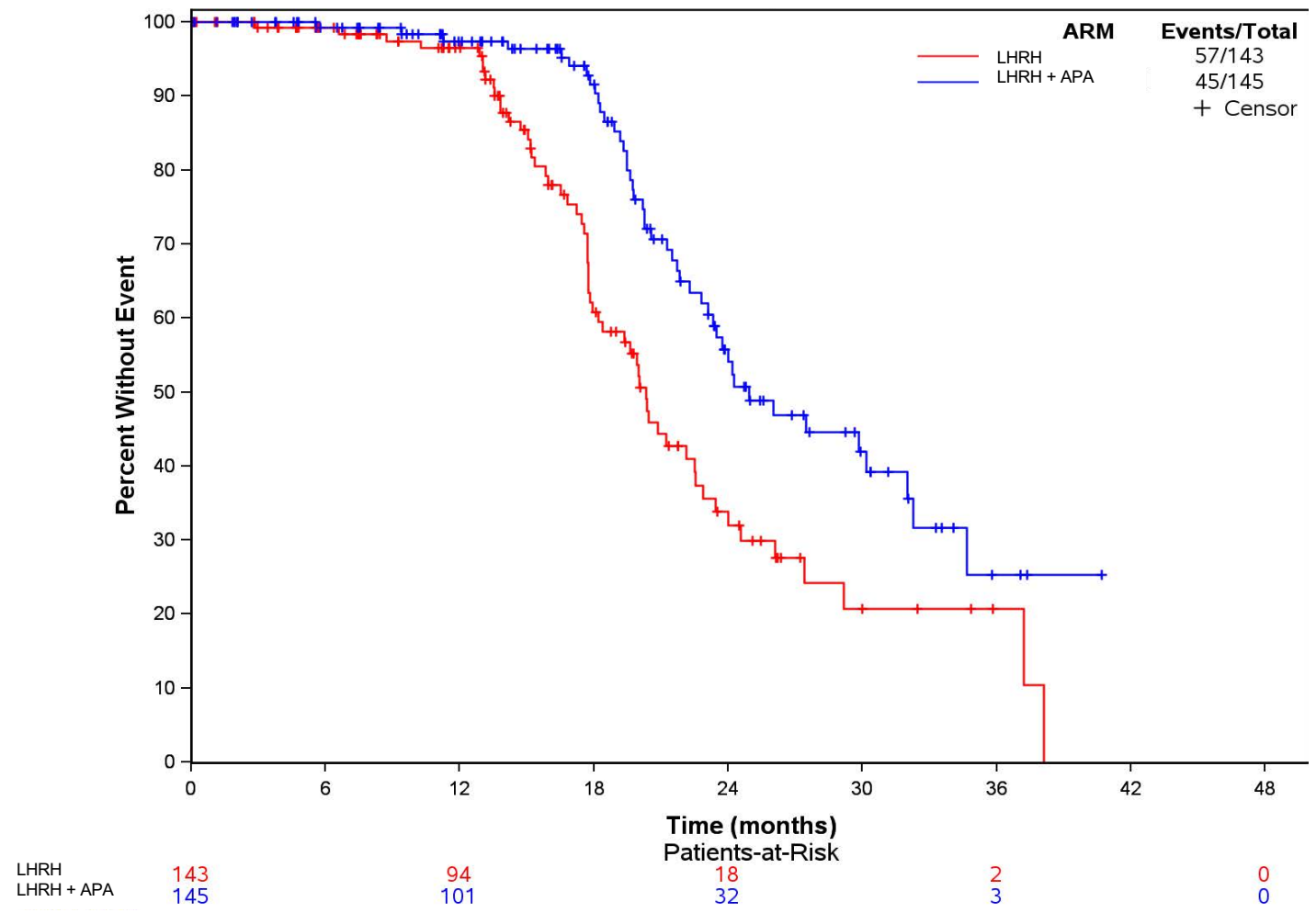


Stratified by PSA doubling time
(< 3 months vs. 3 – 9 months)

52 Weeks

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Arm B: ADT + apalutamide vs. ADT monotherapy



- Median follow up 21.5 months
- 102 PSA PFS events
- Median PSA progression-free survival
  - ADT + APA = 24.9 months (95% CI: 23.3 – 32.3)
  - ADT alone = 20.3 months (95% CI: 18.2 – 22.9)
  - **Hazard ratio 0.52 (95% CI: 0.35 – 0.77)**
  - One-sided p-value = 0.00047)

Aggarwal R et al. ESMO 2022;Abstract LBA63.

EMBARK study design

Patient population:

- Screening PSA ≥1 ng/mL after RP and at least 2 ng/mL above the nadir for primary EBRT
- PSADT ≤9 mo
- No metastases on bone scan or CT/MRI per central read
- Testosterone ≥150 ng/dL
- Prior hormonal therapy ≥9 mo prior to R (neoadjuvant/adjuvant for ≤36 mo OR ≤6 mo for rising PSA)

Stratification factors:

- Screening PSA (≤10 ng/mL vs. >10 ng/mL)
- PSADT (≤3 mo vs. >3 to ≤9 mo)
- Prior hormonal therapy (yes vs. no)

R
1:1:1

N = 1068

Enzalutamide (160 mg oral qd) + leuprolide acetate (22.5 mg IM/q12w)
n = 355
Blinded

Placebo + leuprolide acetate (22.5 mg IM/q12w)
n = 358
Blinded

Enzalutamide monotherapy (160 mg oral qd)
n = 355
Unblinded

PSA <0.2 ng/mL at week 36

Yes → Suspend treatment at week 37 Monitor PSA (reinitiate if PSA rises)[a]

No → Remain on treatment

Primary endpoint[b]:
MFS by BICR, enzalutamide + leuprolide acetate vs. leuprolide acetate alone

Key secondary endpoints[b,c]:

- MFS by BICR, enzalutamide monotherapy vs. leuprolide acetate alone
- Time to PSA progression
- Time to first use of new antineoplastic therapy
- OS[c]

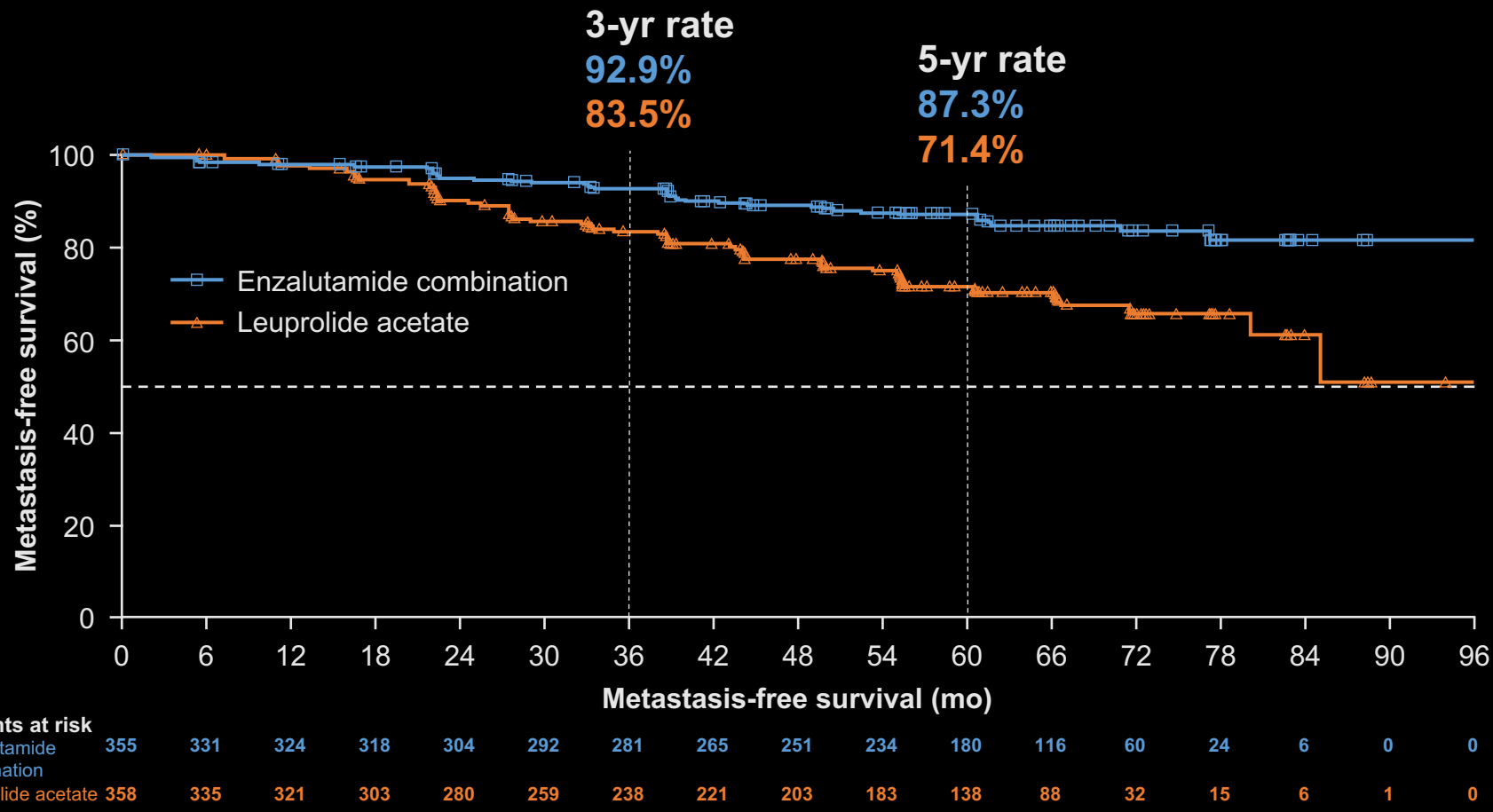
Other secondary endpoints:

- Safety[d]

[a]Study treatment was suspended once at week 37 if PSA was <0.2 ng/mL and restarted when PSA was ≥5.0 ng/mL (without prior RP) and ≥2 ng/mL (prior RP). [b]Intent-to-treat population. [c]Primary endpoint and key secondary endpoints for enzalutamide combination and enzalutamide monotherapy are alpha-protected. *P*-value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints. [d]Safety population. BICR, blinded independent central review; CT, computed tomography; d, day; EBRT, external beam radiotherapy; IM, intramuscular; MFS, metastasis-free survival; mo, month; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time; q, every; R, randomization; RP, radical prostatectomy; w, weeks.

Shore N et al. AUA 2023;Abstract LBA02-09.

Primary endpoint — MFS for enzalutamide combination vs. leuprolide acetate



	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	45 (13)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.42 (0.31–0.61); *P*<0.0001[a]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.47 (0.37–0.67); *P*<0.0001

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value was based on a stratified log-rank. CI, confidence interval; HR, hazard ratio; IWRS, interactive web response system; NR, not reached.

AUA 2023
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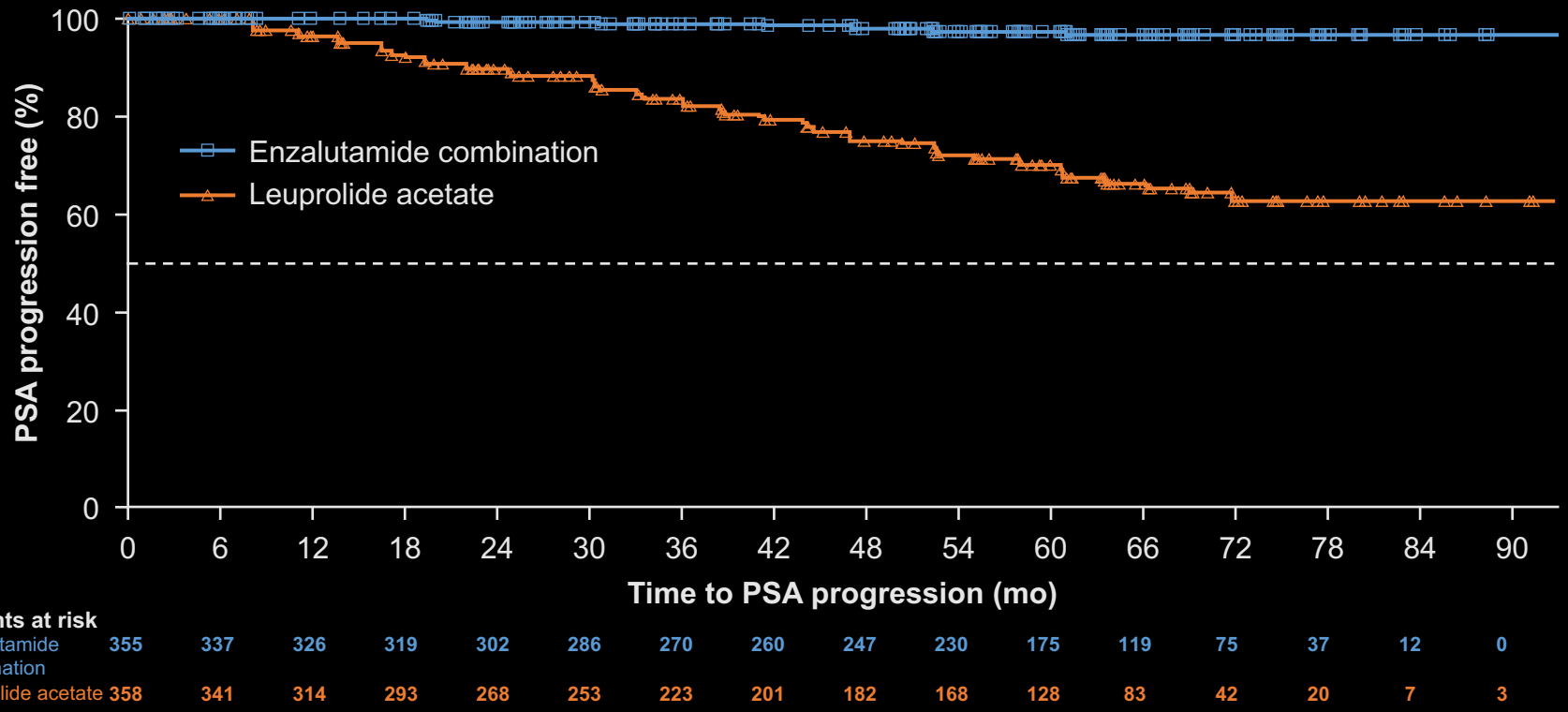
Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

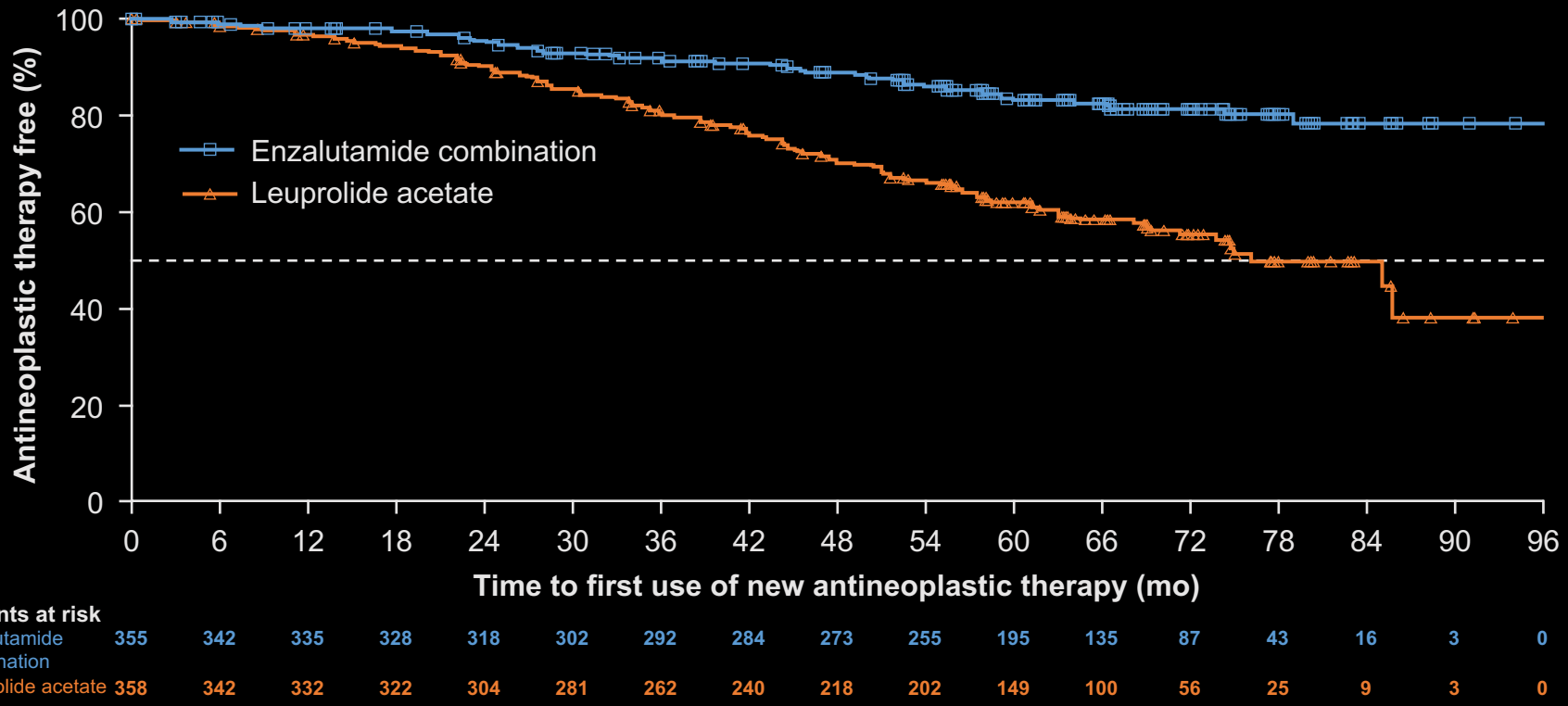
	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

Key secondary endpoint — Time to first use of new antineoplastic therapy for enzalutamide combination vs. leuprolide acetate



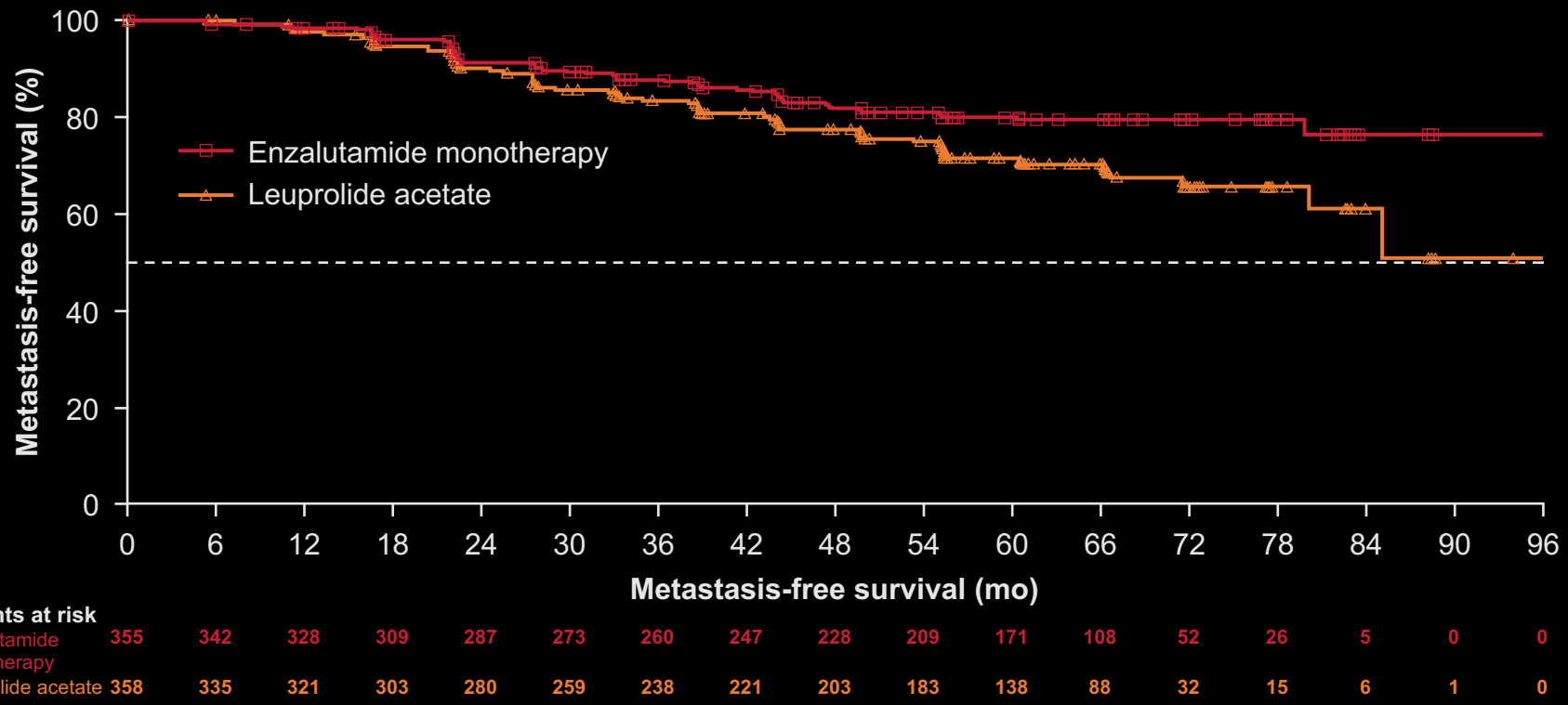
	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	58 (16)	140 (39)
Median time to first use of new antineoplastic therapy (95% CI), mo	NR (NR)	76.2 (71.3–NR)

HR (95% CI): 0.36 (0.26–0.49); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

Key secondary endpoint — MFS for enzalutamide monotherapy vs. leuprolide acetate



	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	63 (18)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.63 (0.46–0.87); *P*=0.0049[a]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.56 (0.40–0.78); *P*=0.0006

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide monotherapy; the two-sided *P*-value was based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

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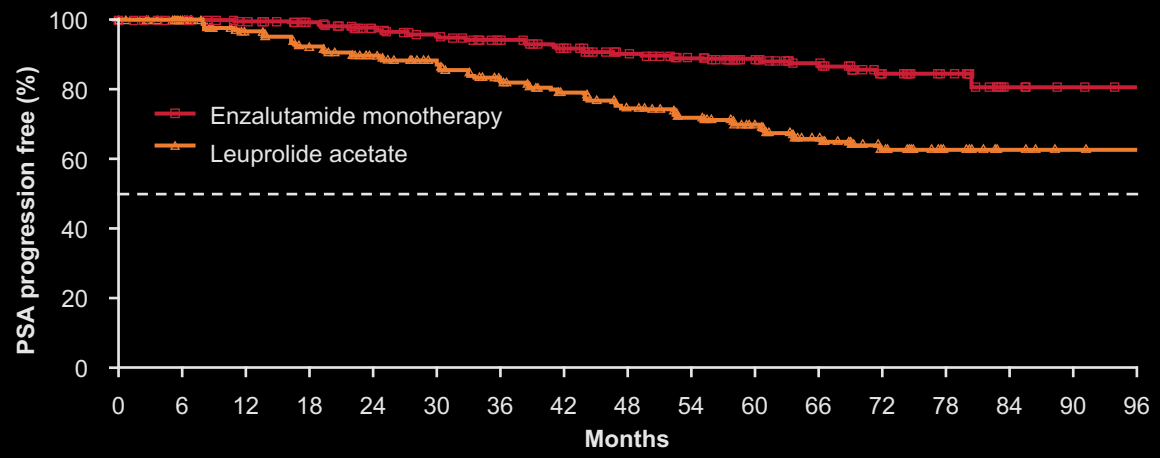
Key secondary endpoints — Enzalutamide monotherapy vs. leuprolide acetate

Time to PSA progression



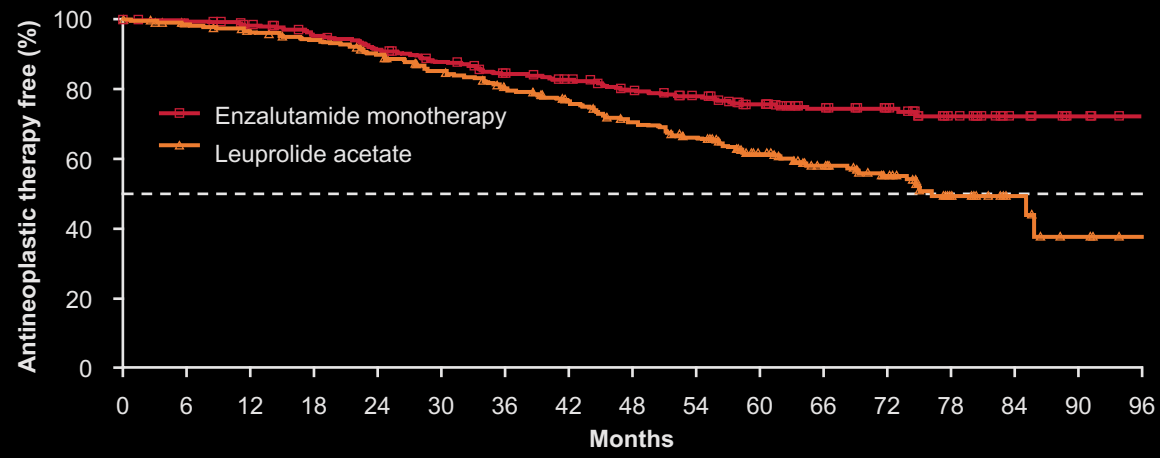
Patients at risk

Enzalutamide monotherapy	355	346	328	311	291	279	262	246	228	213	168	108	63	37	8	3	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3	0

	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	37 (10)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.33 (0.23–0.49); *P*<0.0001[a]

Time to first use of new antineoplastic therapy



Patients at risk

Enzalutamide monotherapy	355	352	341	327	312	297	279	268	252	240	192	124	80	40	12	3	0
Leuprolide acetate	358	342	332	322	304	281	262	240	218	202	149	100	56	25	9	3	0

	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	84 (24)	140 (39)
Median time to first use of new antineoplastic therapy (95% CI), mo	NR (NR)	76.2 (71.3–NR)

HR (95% CI): 0.54 (0.41–0.71); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide monotherapy; the two-sided *P*-value was based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

Safety profile

Event, n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related AE	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious AE	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious AE	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
AE leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
AE leading to permanent discontinuation	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
AE leading to death	6 (1.7)[b]	–	3 (0.8)[b]	–	8 (2.3)[b]	–

- Median treatment duration excluding treatment suspension was 32.4 mo (range, 0.1–83.4 mo) for enzalutamide combination, 35.4 mo (range, 0.7–85.7 mo) for leuprolide acetate, and 45.9 mo (0.4–88.9 mo) for enzalutamide monotherapy.
- The most common AE leading to study drug discontinuation was fatigue (enzalutamide combination, 3.4% [n = 12]; leuprolide acetate, 1.1% [n = 4]; enzalutamide monotherapy, 2.3% [n = 8]).

Data cutoff: January 31, 2023. [a]Percentages may not total 100 because of rounding. Shown are AE that occurred from the time of first dose of study treatment through 30 days after permanent discontinuation. AE were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. [b]Grade 5 AE; none were considered treatment-related. AE, adverse event.

Shore N et al. AUA 2023;Abstract LBA02-09.

Most common TEAEs

Most common TEAEs (>15% of patients), n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hot flash	243 (68.8)	2 (0.6)	203 (57.3)	3 (0.8)	77 (21.8)	1 (0.3)
Fatigue	151 (42.8)	12 (3.4)	116 (32.8)	5 (1.4)	165 (46.6)	14 (4.0)
Arthralgia	97 (27.5)	5 (1.4)	75 (21.2)	1 (0.3)	81 (22.9)	1 (0.3)
Hypertension	82 (23.2)	2 (0.6)	69 (19.5)	0	67 (18.9)	0
Fall	74 (21.0)	3 (0.8)	51 (14.4)	2 (0.6)	56 (15.8)	5 (1.4)
Back pain	60 (17.0)	1 (0.3)	54 (15.3)	0	62 (17.5)	1 (0.3)
Nausea	42 (11.9)	0	29 (8.2)	0	54 (15.3)	1 (0.3)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0

- The most common AEs (>15% of patients) for all treatment cohorts were hot flash, fatigue; plus gynecomastia in the enzalutamide monotherapy cohort; most were grade <3.

Data cutoff: January 31, 2023. [a]Percentages may not total 100 because of rounding. Shown are AEs that occurred from the time of first dose of study treatment through 30 days after permanent discontinuation. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. TEAE, treatment-emergent AE.

Shore N et al. AUA 2023;Abstract LBA02-09.

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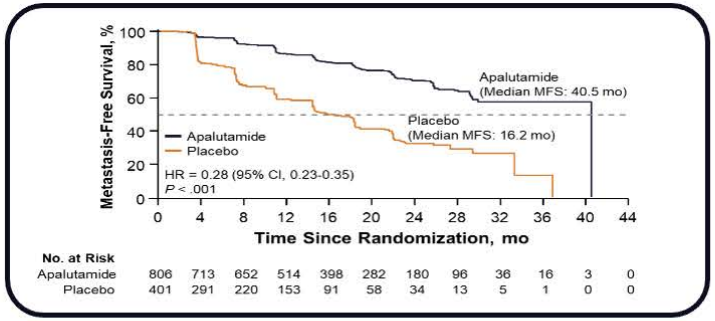
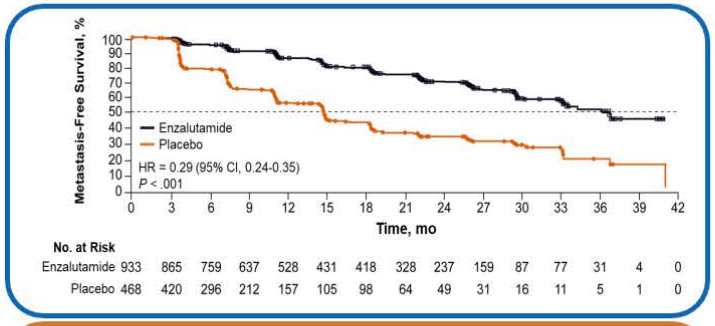
Role of AR Pathway Inhibitors in Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC)

SPARTAN[1]
Apalutamide



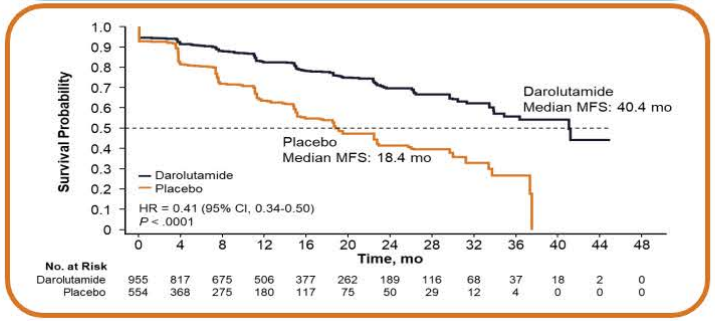
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

PROSPER[2]
Enzalutamide



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- 22-month MFS benefit

ARAMIS[3]
Darolutamide



- 59% reduction of distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

1. Smith MR et al. *N Engl J Med*. 2018;378:1408-1418. 2. Hussain M et al. *N Engl J Med*. 2018;378:2465-2474.
3. Fizazi K et al. *N Engl J Med*. 2019;380:1235-1246.

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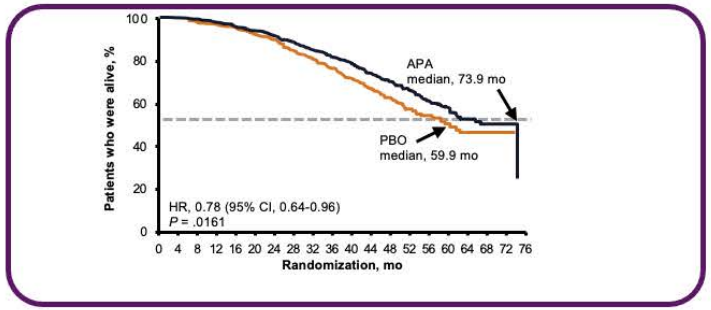
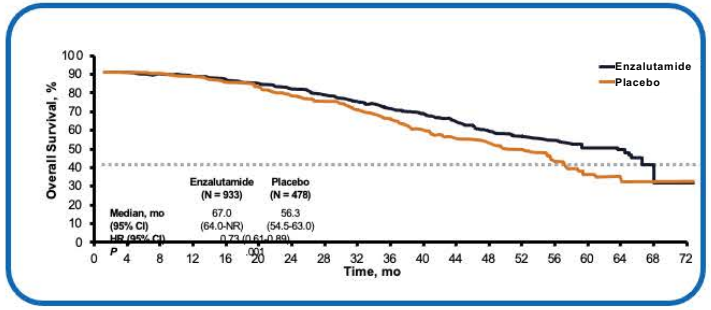
Role of AR Pathway Inhibitors in Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC)

SPARTAN[1]
Apalutamide



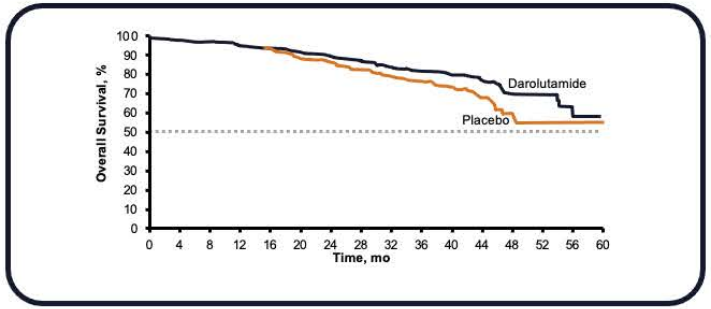
- 22% reduction in risk of death
- Median follow-up of 52.0 mo
- Median OS was significantly longer for apalutamide vs placebo
  - 73.9 mo vs 59.9 mo
  - **HR = 0.78 (95% CI 0.64-0.96); *P* = .016**

PROSPER[2]
Enzalutamide



- 27% reduction in risk of death
- Median follow-up of 48 mo
- Median OS was significantly longer for enzalutamide vs placebo
  - 67.0 mo vs 56.3 mo
  - **HR = 0.73 (95% CI 0.61-0.89); *P* = .001**

ARAMIS[3]
Darolutamide



- 31% reduction in risk of death
- Median follow-up of 29.0 mo
- Median OS was significantly longer for darolutamide vs placebo
  - **HR = 0.69 (95% CI, 0.53-0.88); *P* = .003**

1. Smith MR et al. *Eur Urol*. 2021;79:150-158. 2. Sternberg CN et al. *N Engl J Med.* 2020; 382:2197-2206.
3. Fizazi K et al. *N Engl J Med*. 2020;383:1040-1049.

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Level 1 Evidence for Improved Overall Survival in mCSPC

Studies	Intervention	Control	Comments
GETUG-15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar benefits for recurrent and de novo metastatic disease
PEACE-1	Abiraterone +ADT + docetaxel (+/- prostate radiation)	ADT + docetaxel (+/- prostate radiation)	Subgroup analysis

Parker et al Lancet 2018; Armstrong et al JCO 2021; Davis et al NEJM 2019; James N et al Lancet 2015; Sweeney et al NEJM 2015; Chi KN et al NEJM 2019; Fizazi K et al NEJM 2017; James et al NEJM 2017; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

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ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

Patients (N=1306)
- mHSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratification
- Extent of disease: M1a vs M1b vs M1c
- ALP < vs ≥ ULN

Docetaxel × 6

Darolutamide 600 mg twice daily + ADT

Placebo twice daily + ADT

Docetaxel × 6

FPFV: Nov 2016
LPFV: June 2018

Data cut-off
Oct 25, 2021

Endpoints

Primary: OS

Secondary
- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

***One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.**

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

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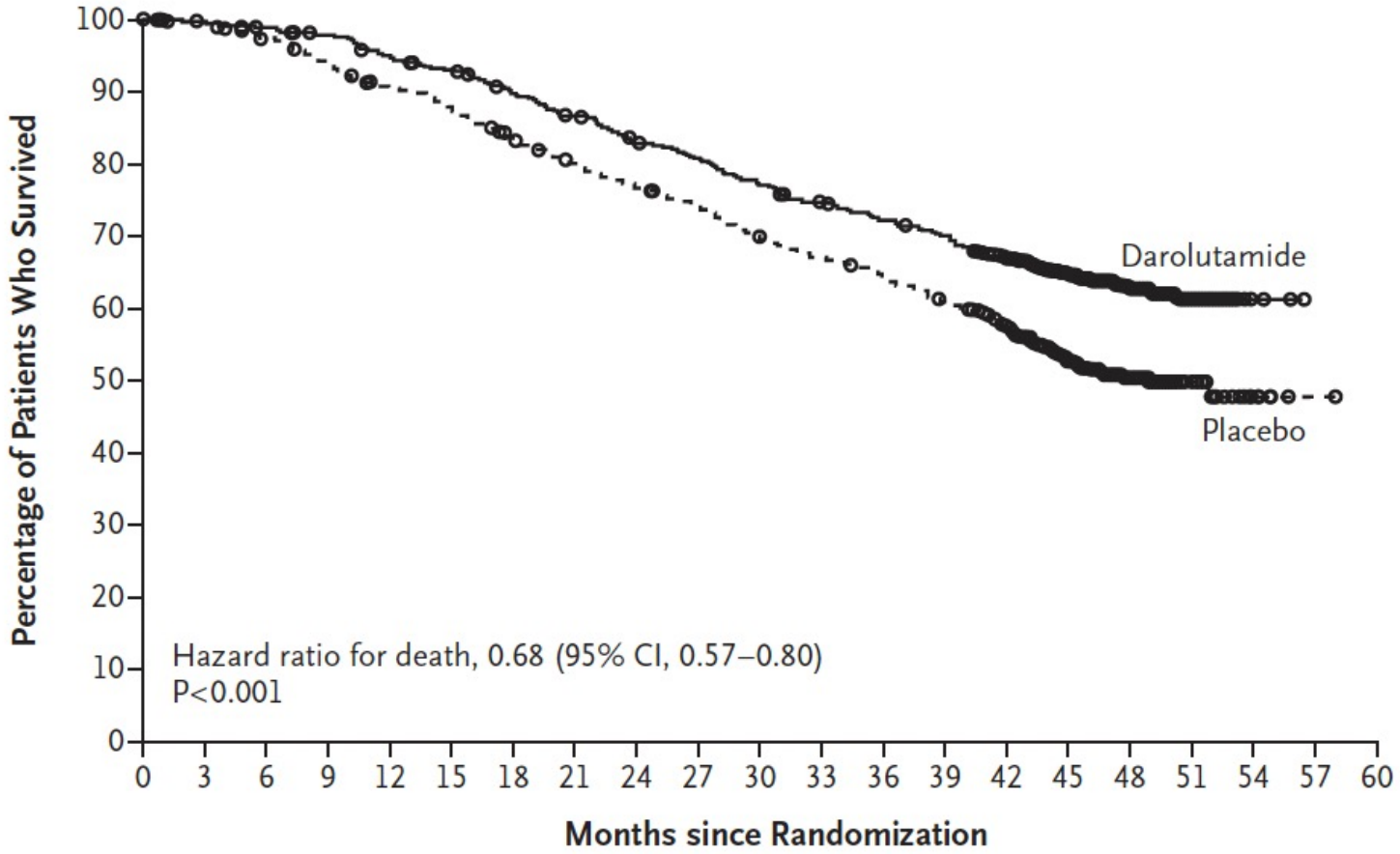
ARASENS Primary Endpoint: Overall Survival



	Median Survival (95% CI) *mo*
Darolutamide	NE
Placebo	48.9 (44.4–NE)

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

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

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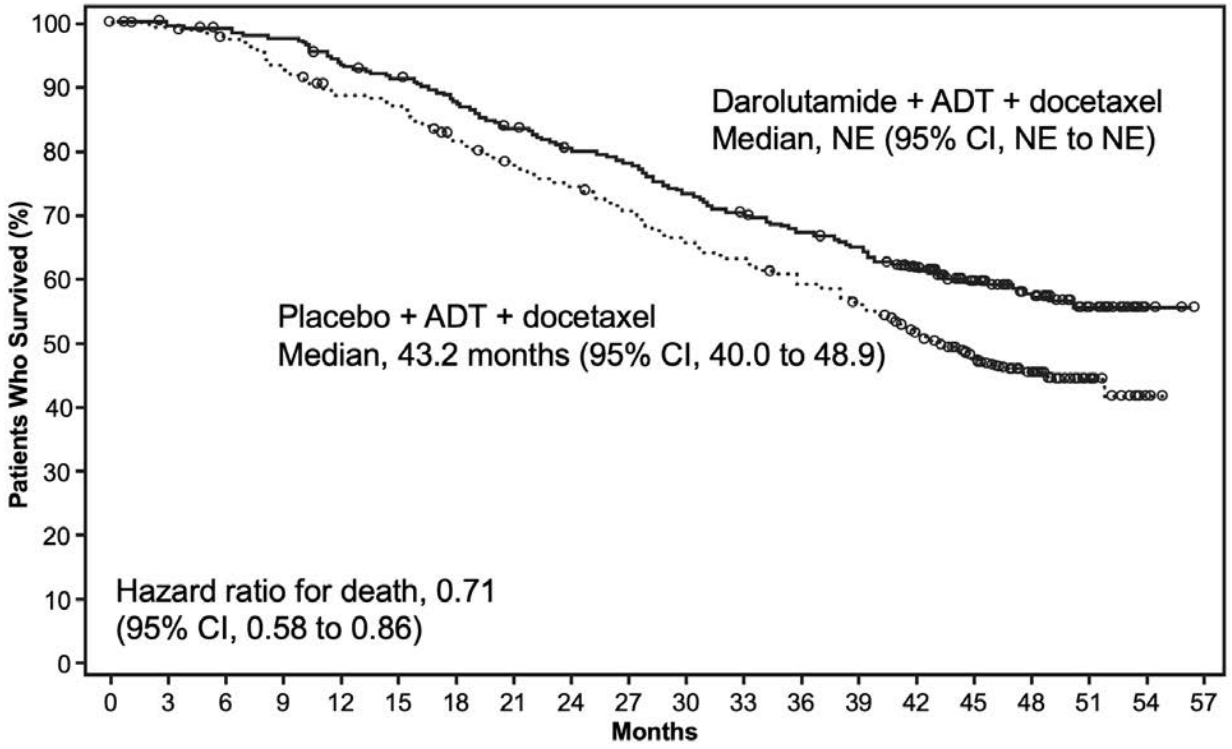
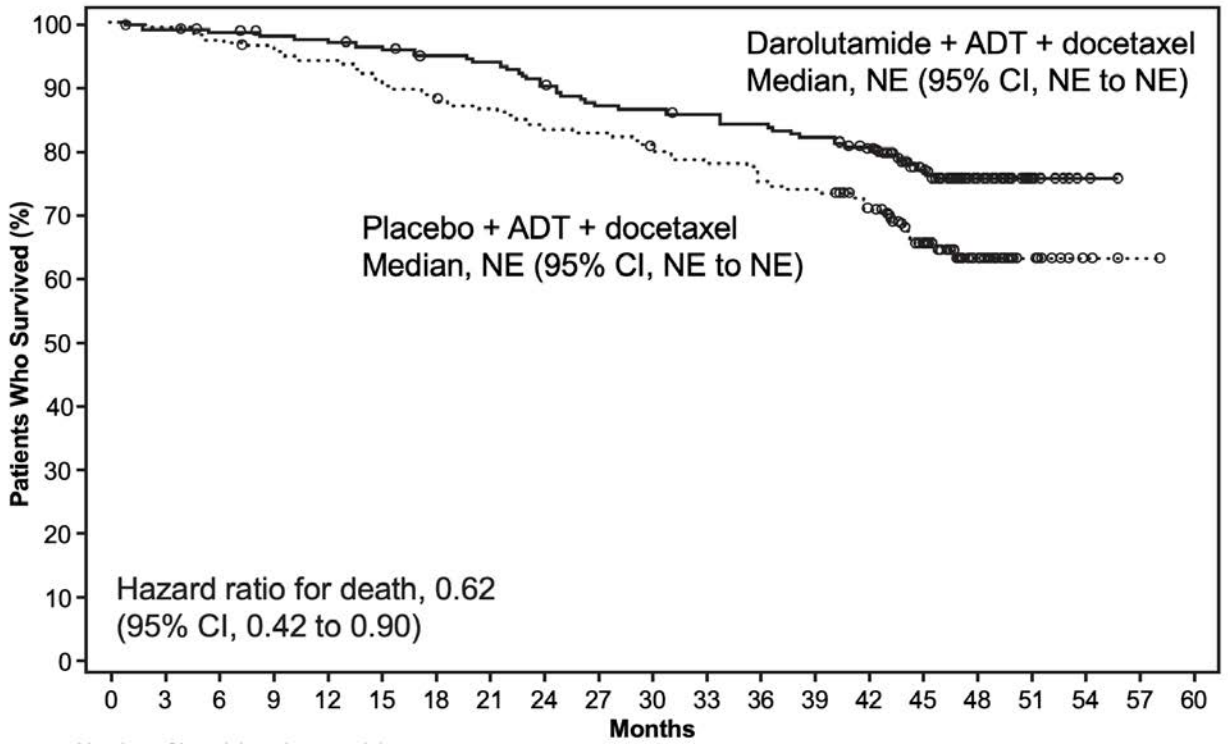
ARASENS: Overall Survival by Risk Group

High-Risk Group



Low-Risk Group



Hussain *et al* (2023) J Clin Oncol ascopubs.org/doi/full/10.1200/JCO.23.00041

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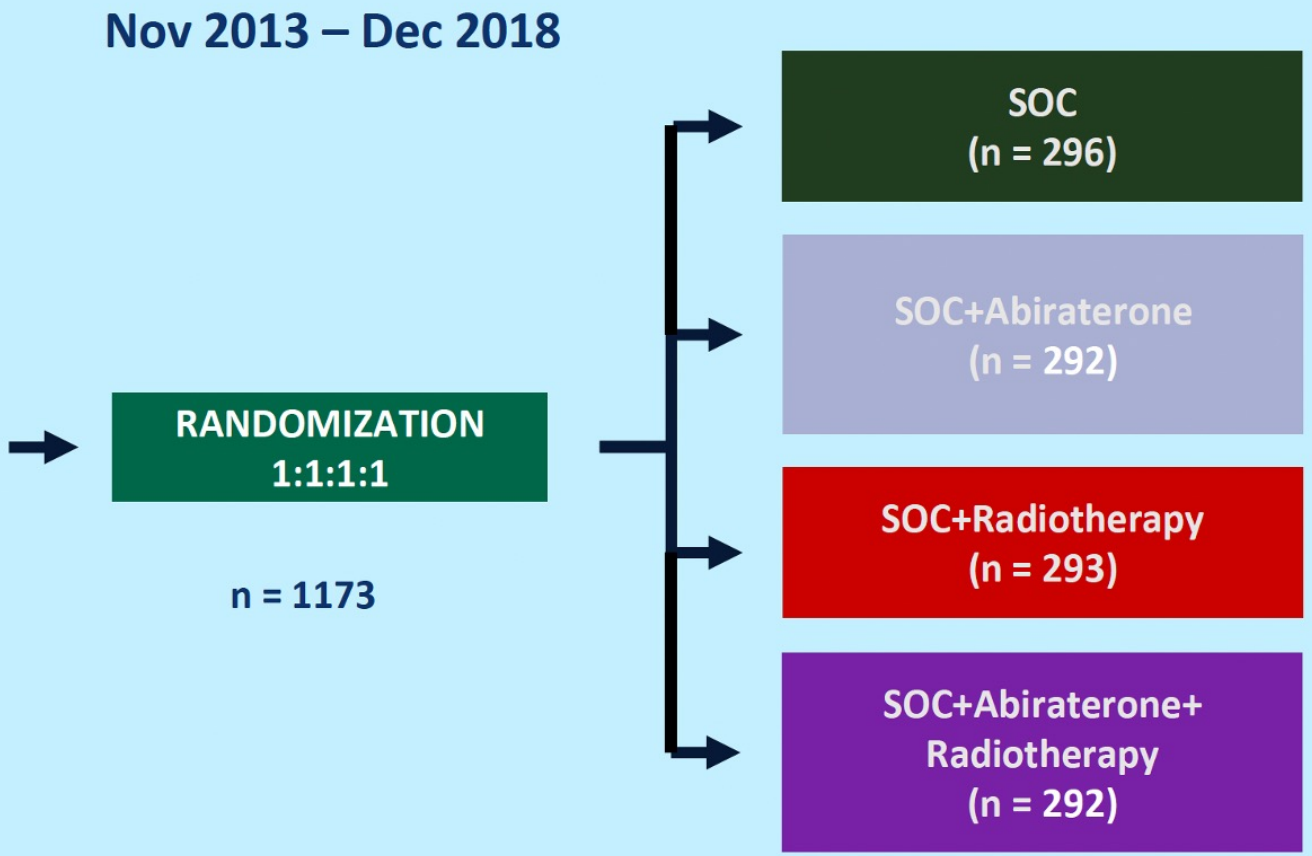
PEACE-1 Study Design

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

2021 ESMO congress

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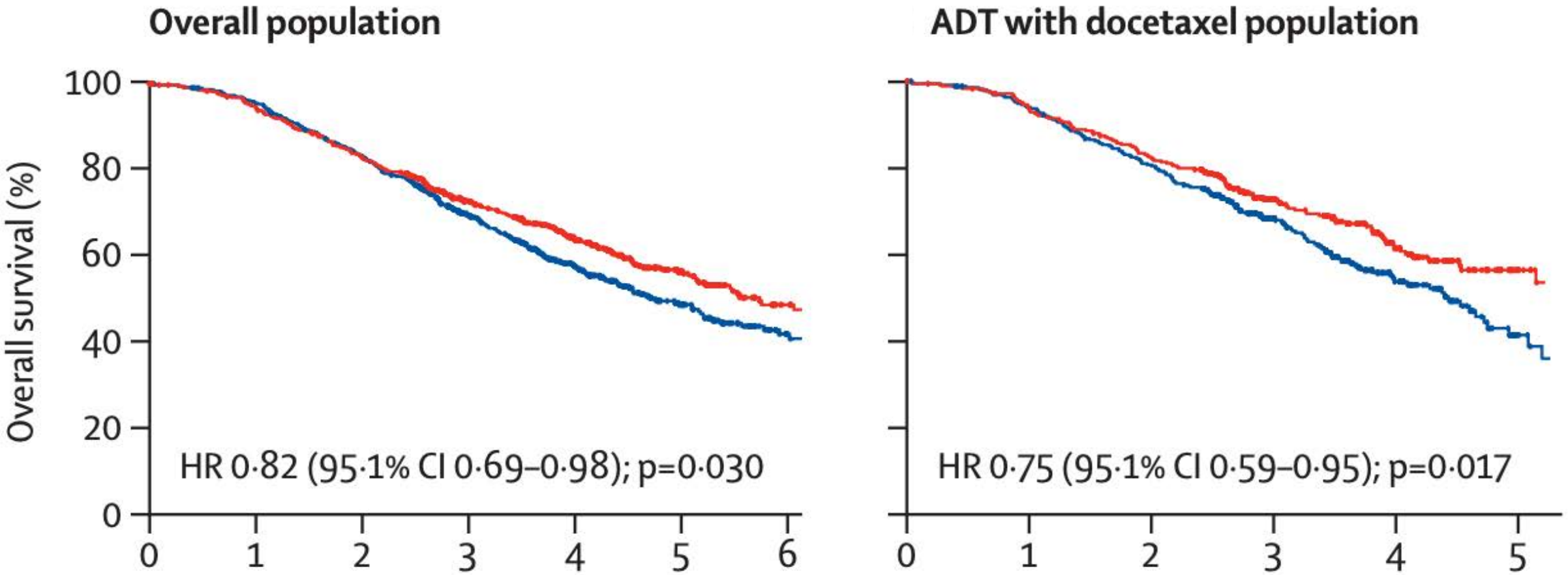
PEACE-1: Overall Survival



Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

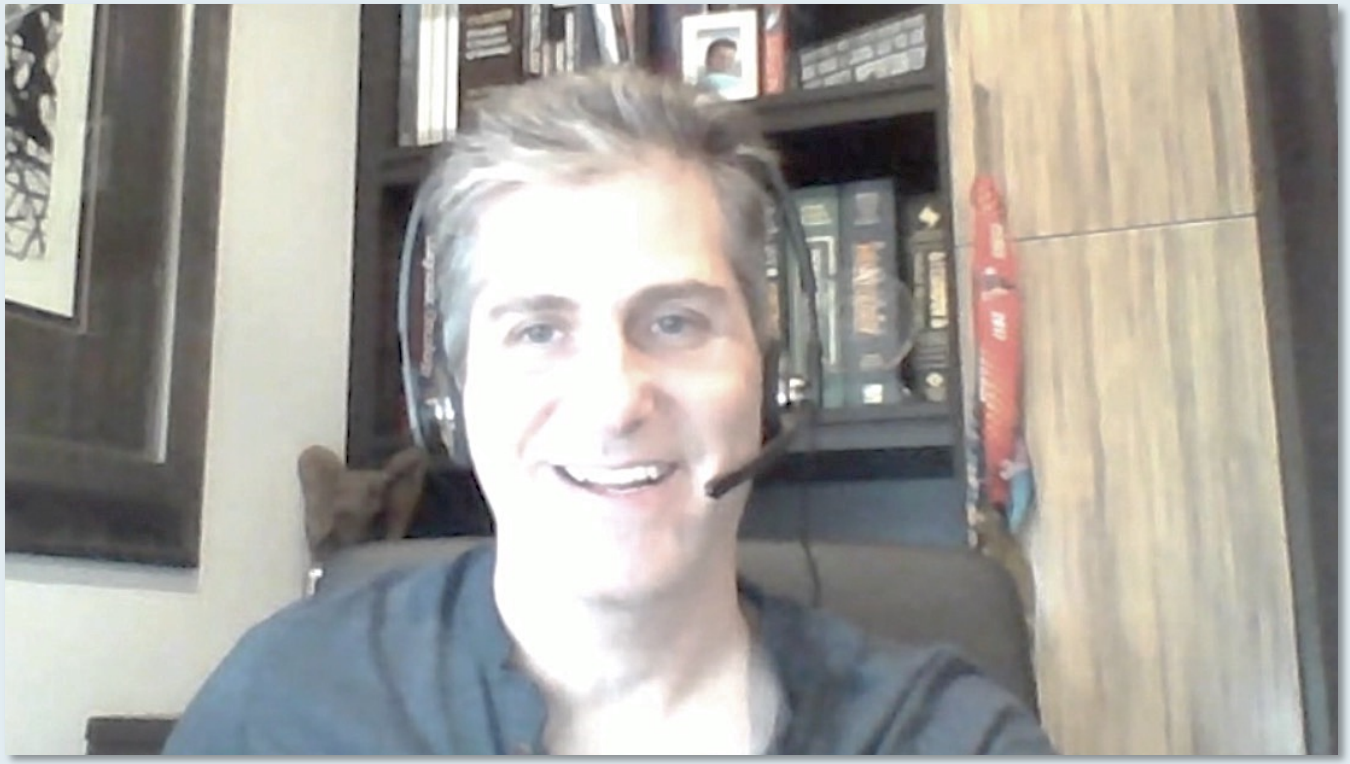
Conclusions

AR pathway inhibitors (ARPIs) have an important role across a broad range of prostate cancer disease states:

- Abiraterone and enzalutamide improve rPFS and OS in mCRPC, either before or after chemotherapy
- Apalutamide, enzalutamide and darolutamide improve MFS and OS in nmCRPC
- Abiraterone, apalutamide, enzalutamide and darolutamide improve OS in mCSPC
- Abiraterone improves MFS and OS in high-risk primary and recurrent nmCSPC
- Enzalutamide improves MFS in recurrent nmCSPC

Clinical Questions and Cases

Case Presentation: 86-year-old man with M0 CRPC and multiple progressions treated with ADT/daralutamide



Dr Shachar Peles (Lake Worth, Florida; 10-8-2021)

RTP RESEARCH TO PRACTICE

Prostate Cancer
Optimizing Endocrine Treatment

- **Management of higher-risk nonmetastatic prostate cancer**
  - **Role of treatment intensification (androgen receptor inhibitors)**
  - **Role of androgen receptor inhibitors without ADT (enzalutamide)**
- **Intermittent endocrine-based therapy**
- **Front-line treatment for patients presenting with metastatic disease and those who develop metastases after local treatment only (hormone-sensitive metastatic disease)**

RTP
RESEARCH
TO PRACTICE

Discussion Question

Regulatory and reimbursement issues aside, in general, what is your preferred ADT for a patient with PSA-only (M0) recurrence?

Discussion Question

In general, for a patient with nonmetastatic hormone-sensitive prostate cancer with biochemical recurrence that is considered high risk (eg, PSA doubling time ≤9 months), which endocrine therapy would you most likely recommend?

Discussion Question

Regulatory and reimbursement issues aside, do you believe enzalutamide monotherapy should be offered to men about to begin treatment for hormone-sensitive prostate cancer with high-risk biochemical recurrence?

Discussion Question

In general, in which situations do you use intermittent (as opposed to continuous) endocrine treatment for patients with prostate cancer?

RTP
RESEARCH
TO PRACTICE

Discussion Question

A 70-year-old man s/p radical prostatectomy for high-risk localized prostate cancer is found to have asymptomatic, low-volume nonvisceral metastatic disease 2 years later. Genetic testing is negative for homologous recombination repair (HRR) mutations. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

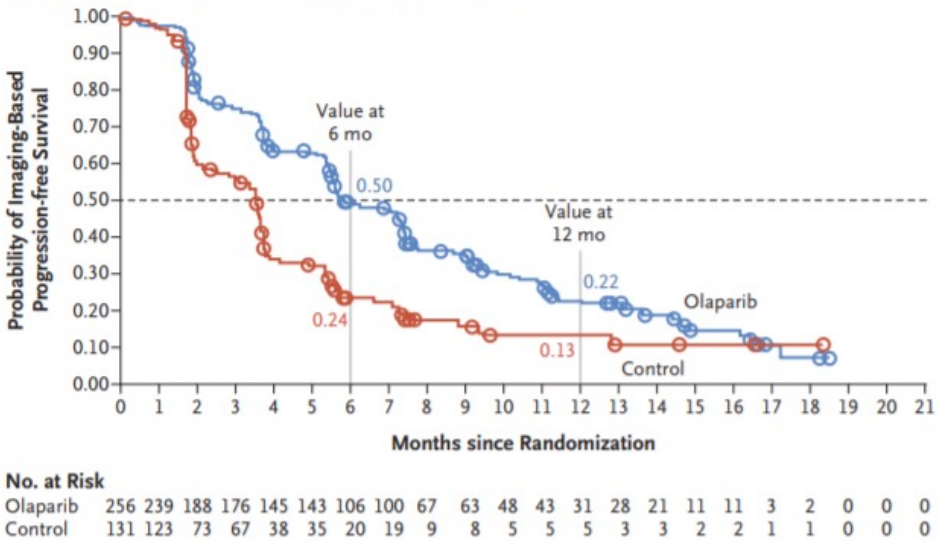
Evidence Based Use of Other Therapeutic Approaches in mCRPC

Alicia Morgans, MD, MPH
Associate Professor of Medicine,
Harvard Medical School
Medical Director Survivorship Program,
Dana-Farber Cancer Institute

Dana-Farber
Cancer Institute

PROfound Study: PFS and OS

PFS Overall



	Median (mo)
Olaparib	5.8
Control	3.5

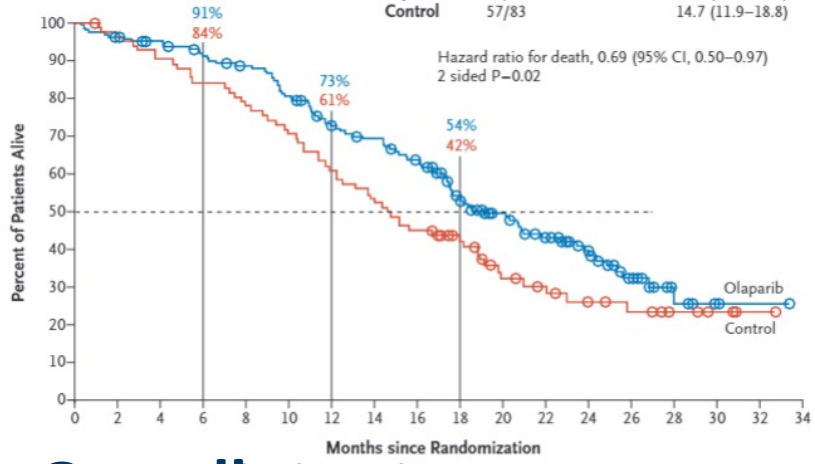
Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001

de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

Overall Survival

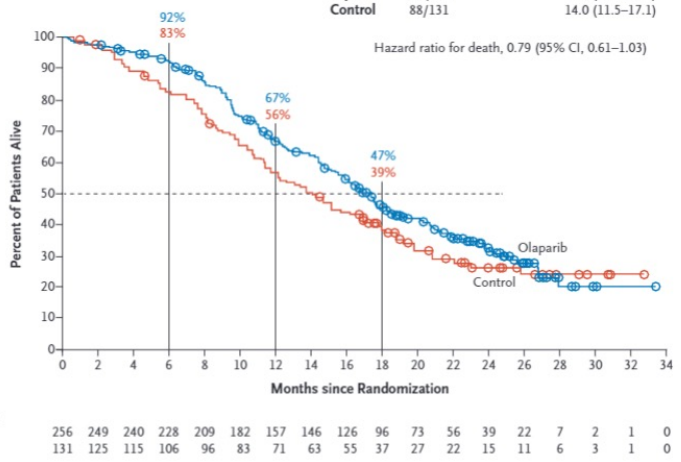
Cohort A

	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) mo
Olaparib	91/162	19.1 (17.4–23.4)
Control	57/83	14.7 (11.9–18.8)



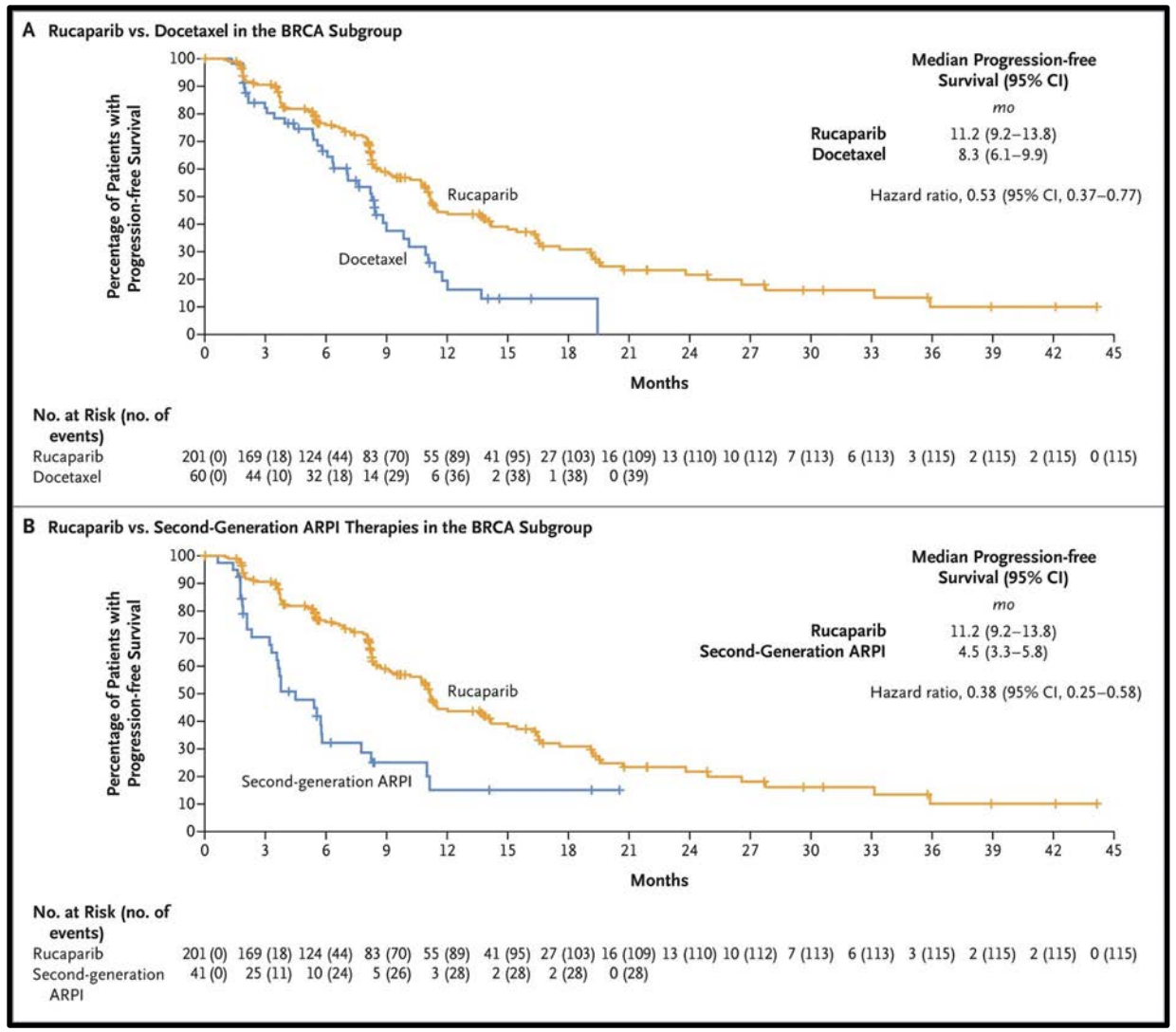
Overall

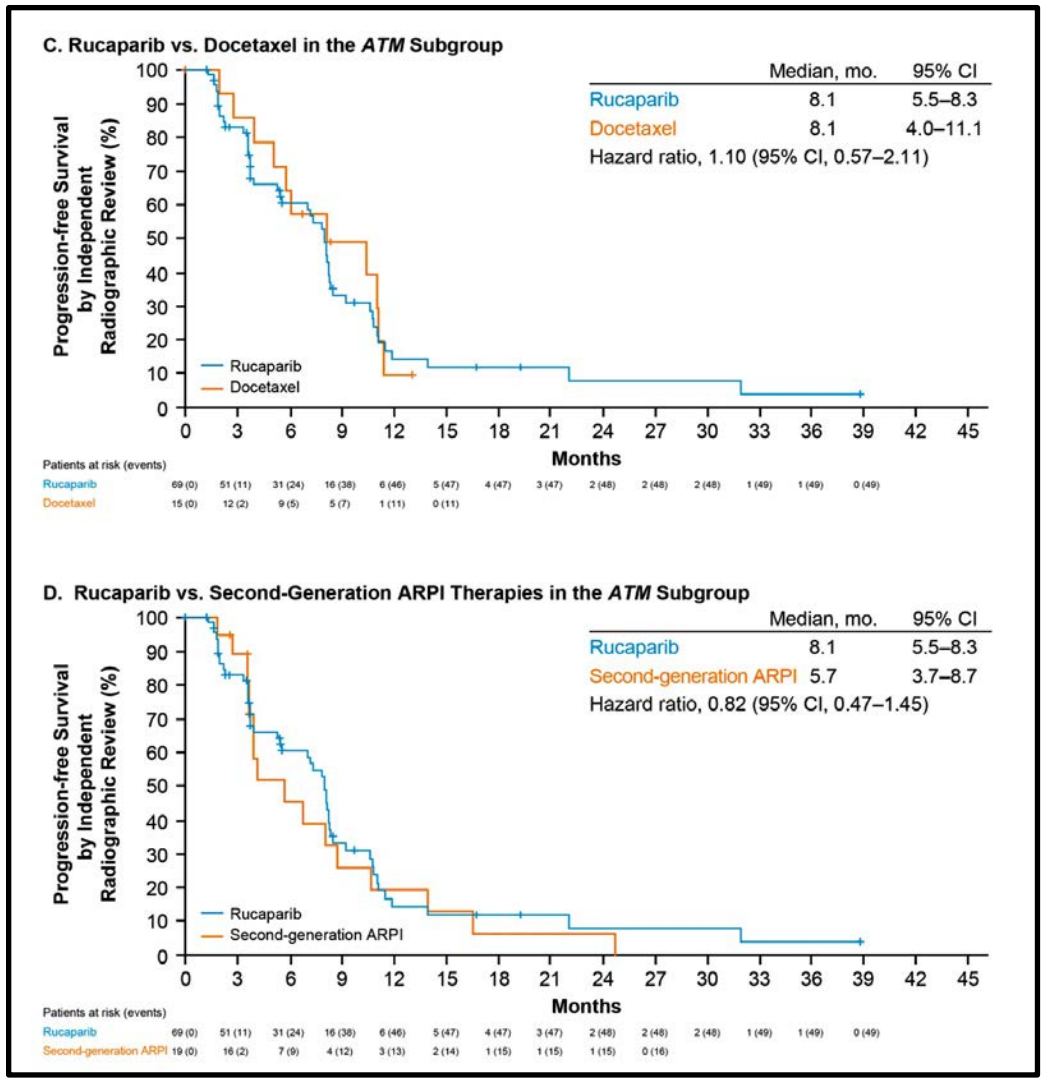
	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) mo
Olaparib	160/256	17.3 (15.5–18.6)
Control	88/131	14.0 (11.5–17.1)



Hussain M et al. *N Engl J Med*. 2020;383:2345-2357.

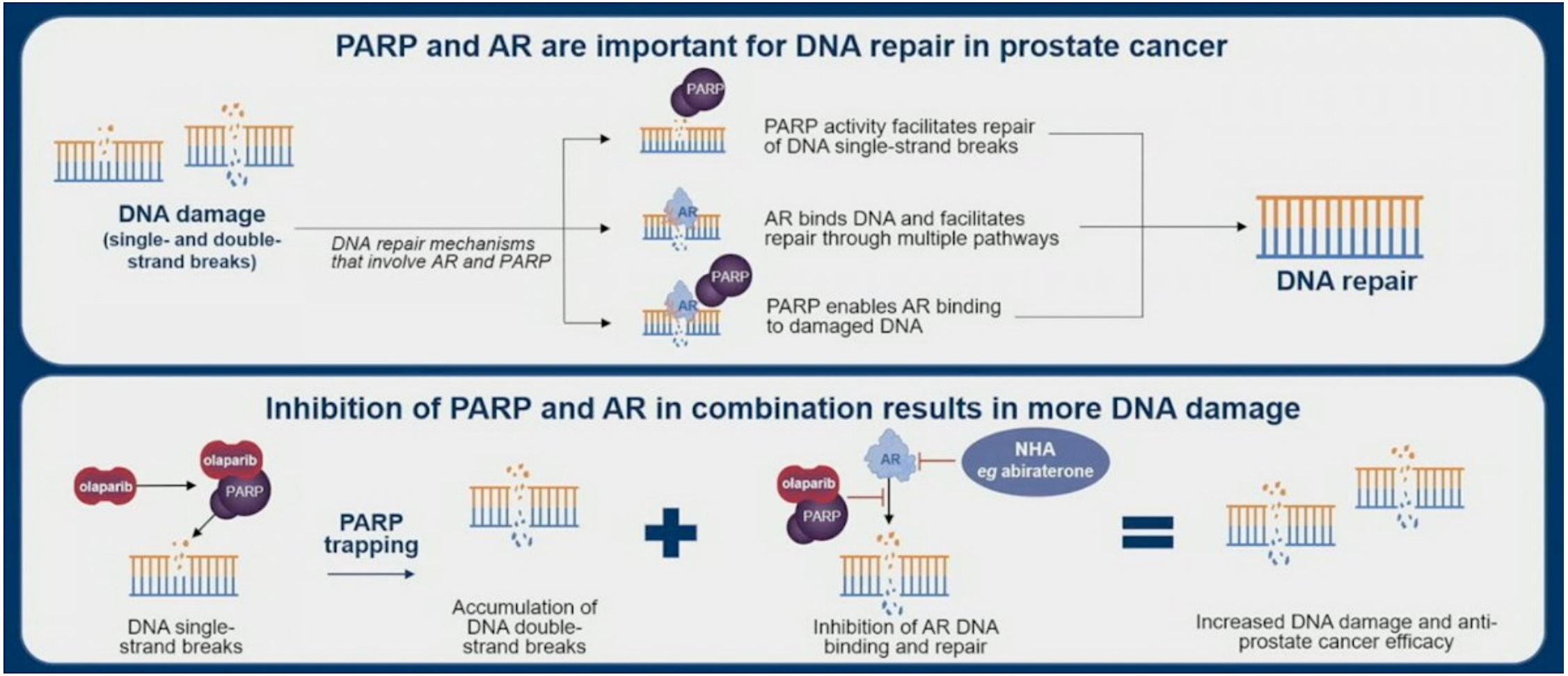
TRITON3 Study: Rucaparib vs Physician's Choice in Patients with *BRCA1/2* or *ATM* Alterations





Fizazi K et al. *New Engl J Med.* 2023;388:719–32.

Interactions between PARP signaling and AR signaling



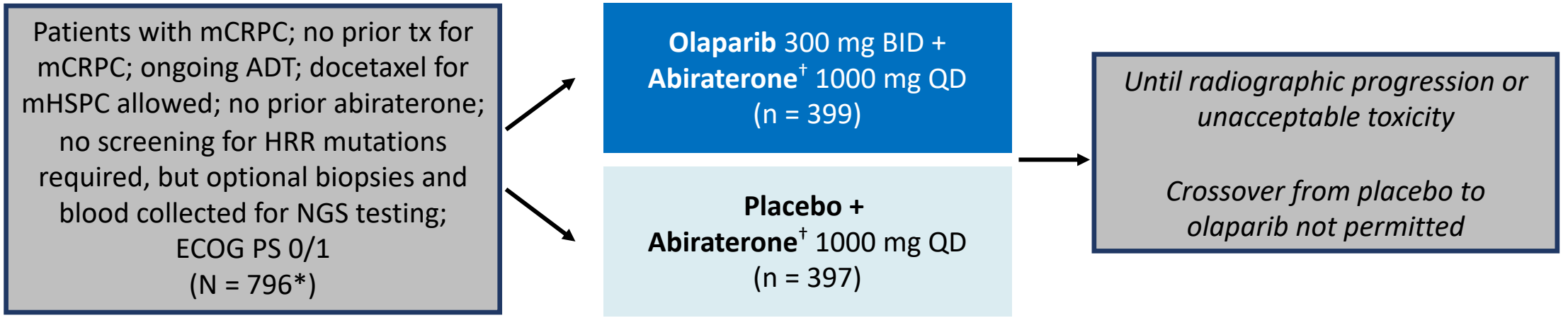
Clarke N, et al. GU ASCO 2023.

Clarke N, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evidence 2022.EVIDoa2200043

PROpel: First-Line Olaparib + Abiraterone vs Placebo + Abiraterone in mCRPC

- Interim analysis of international, randomized, double-blind phase III trial (data cutoff: July 30, 2021)

Stratified by metastatic disease sites (bone only vs visceral vs other), taxane for mHSPC (yes vs no)



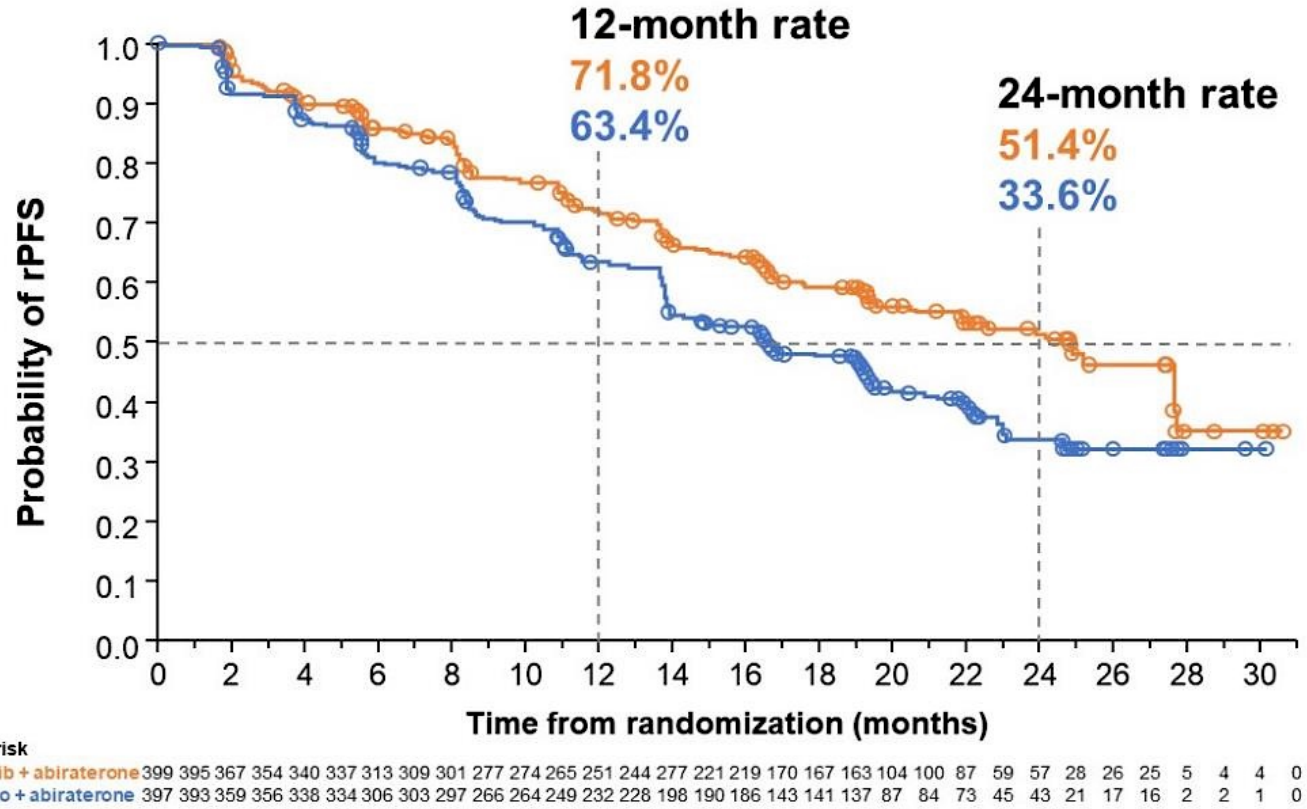
*An additional 108 patients will be randomized 1:1 in China.
†Prednisone/prednisolone (5 mg BID) given with abiraterone.

- **Primary endpoint:** rPFS by investigator
- **Key secondary endpoints:** OS, time to subsequent therapy or death, PFS2, ORR, HRRm prevalence (retrospectively assessed), HRQOL, safety

Saad F, et al. ASCO GU 2022. Abstract 11; Clarke NW, et al. ASCO 2019. Abstract TPS340; ClinicalTrials.gov ID: NCT03732820.

PROpel: rPFS by INV-Assessment—Primary Endpoint

34% risk reduction of progression or death with olaparib + abiraterone



	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*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

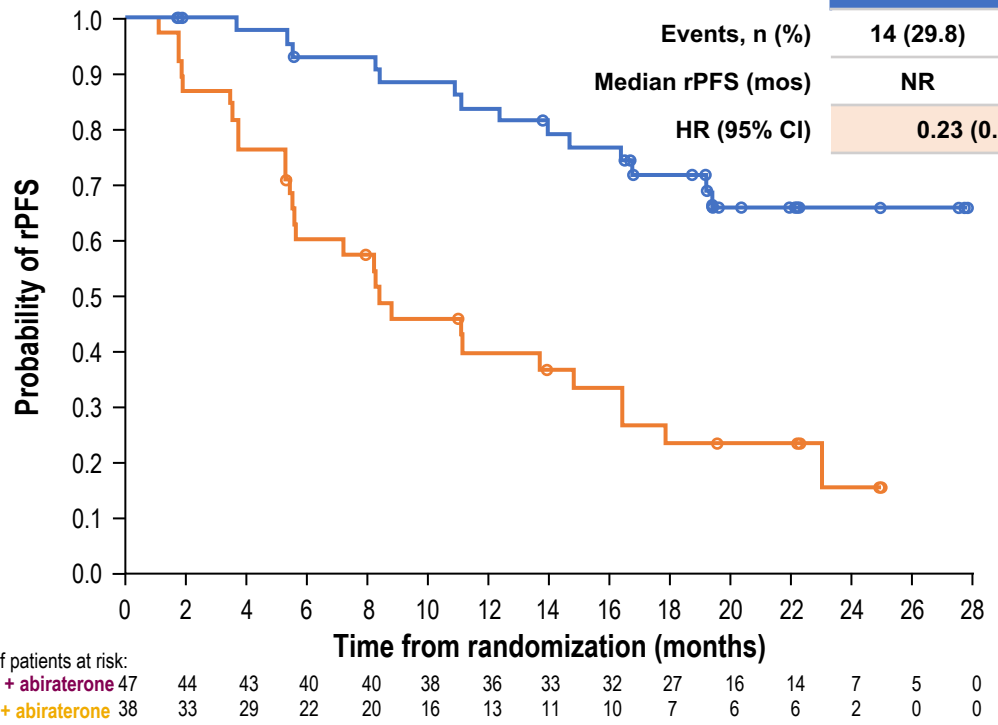
Saad F, et al. ASCO GU Ca Symp 2022. Abstract 11.
Clarke et al. *NEJM Evidence*.2022;1(9): EVIDoa2200043

An rPFS benefit was observed with olaparib + abiraterone across BRCAm and non-BRCAm subgroups

While the greatest benefit was observed in the BRCAm subgroup, there was an independent, clinically meaningful rPFS benefit of 5 months in the non-BRCAm subgroup

BRCAm subgroup (investigator assessment)

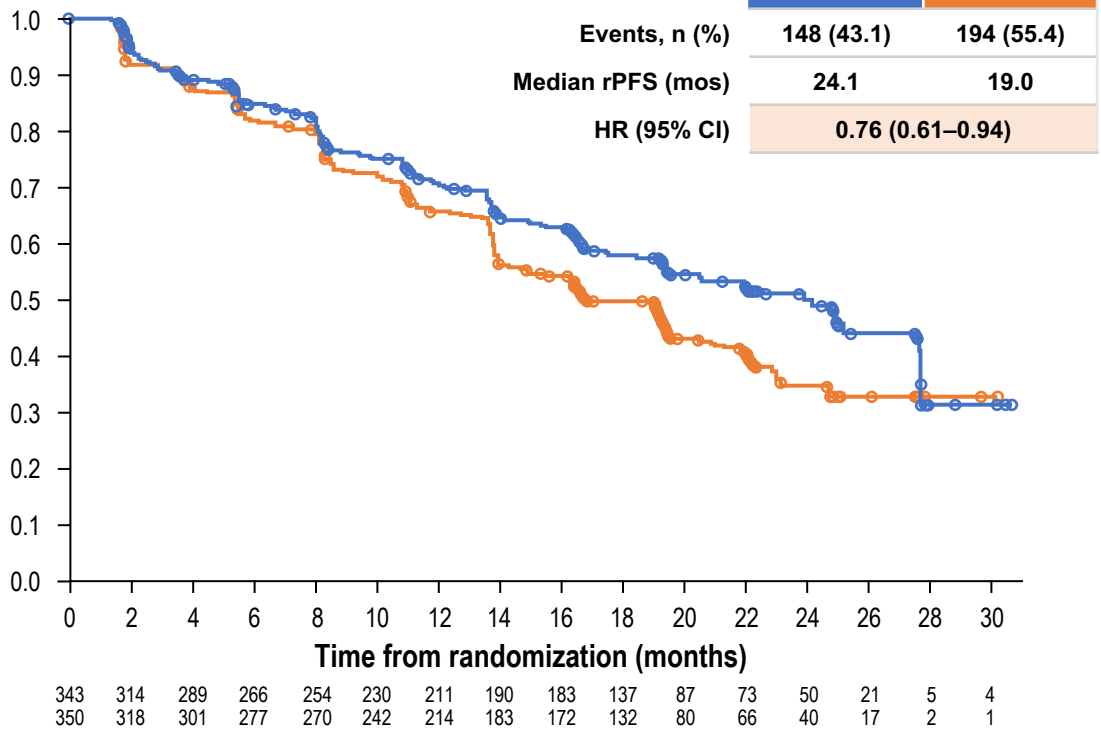
	Olaparib + abiraterone (n=47)	Placebo + abiraterone (n=38)
Events, n (%)	14 (29.8)	28 (73.7)
Median rPFS (mos)	NR	8.4
HR (95% CI)	0.23 (0.12–0.43)	



Sensitivity analysis by ***blinded independent central review***:
Median NR vs 8.4 months;
HR 0.18, 95% CI 0.09–0.34

Non-BRCAm subgroup (investigator assessment)

	Olaparib + abiraterone (n=343)	Placebo + abiraterone (n=350)
Events, n (%)	148 (43.1)	194 (55.4)
Median rPFS (mos)	24.1	19.0
HR (95% CI)	0.76 (0.61–0.94)	

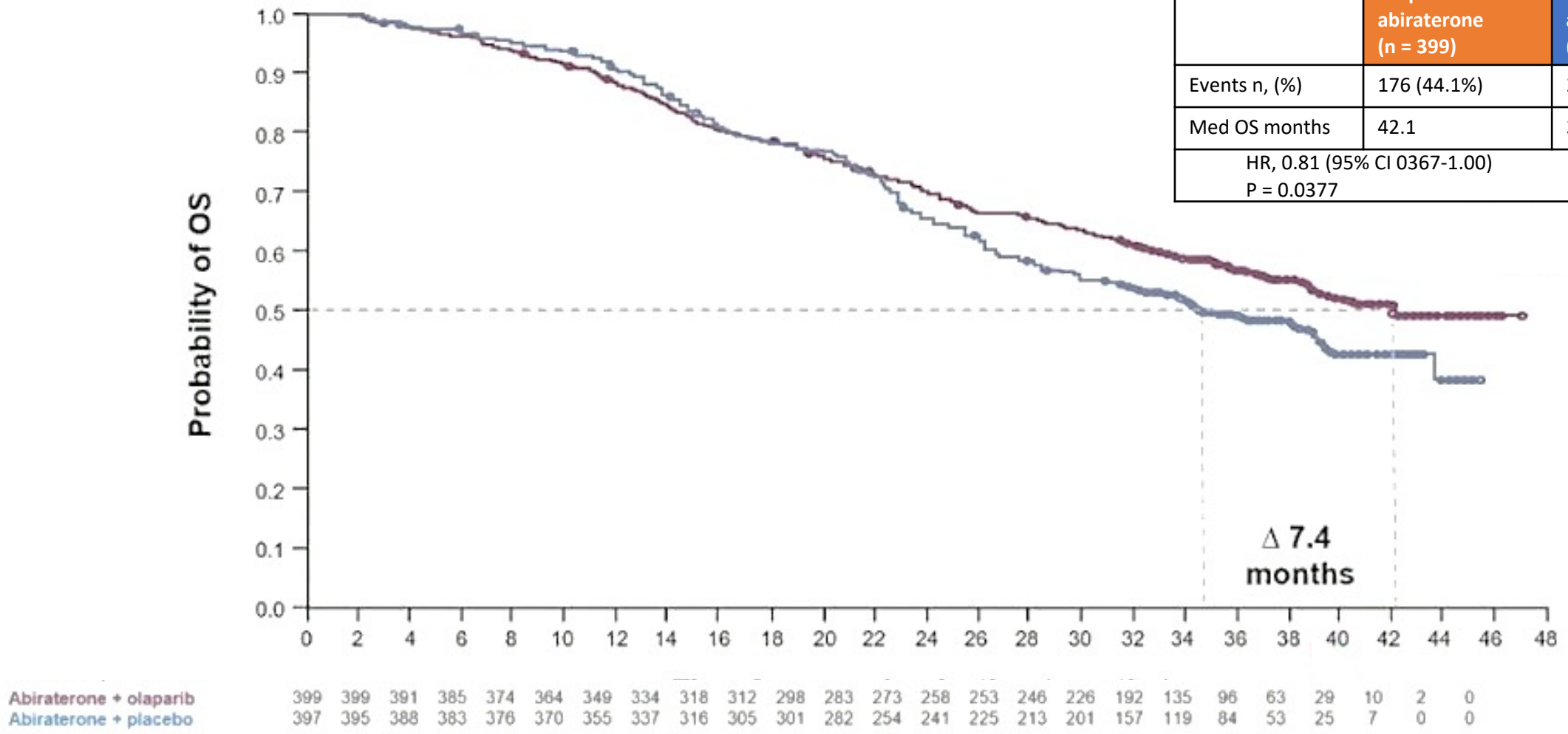


Sensitivity analysis by ***blinded independent central review***:
Median 27.6 vs 16.6 months;
HR 0.72, 95% CI 0.58–0.90

BRCA2m: HR 0.25, 95% CI 0.12–0.48. Non-BRCA2m: HR 0.74, 95% CI 0.60–0.92. Patient enrolment was not based on HRRm status; however, the HRRm and BRCAm status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma ctDNA HRRm tests. This subgroup analysis is *post hoc* exploratory analysis. A circle indicates a censored observation.
DCO1: 30 July 2021. BICR=Blinded Independent Central Review; CI=confidence interval; DCO1=first data cut-off; HR=hazard ratio; NR=not reached; rPFS=radiographic progression-free survival.Results from the first data cut-off at primary analysis: 30 July 2021. 1. Saad F, et al. Presented at ESMO 9th–13th September 2022, Paris, France. Presentation #13570.

ASCO GU 2023 - PROpel: Final OS Analysis – ITT Population

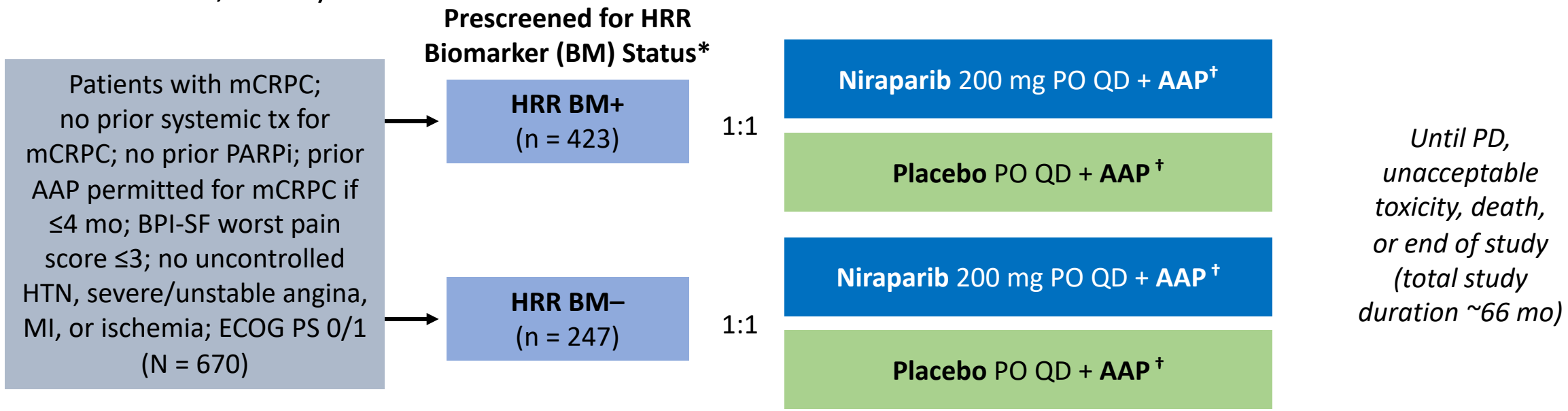
	Olaparib + abiraterone (n = 399)	Placebo + abiraterone (n = 397)
Events n, (%)	176 (44.1%)	205 (51.6%)
Med OS months	42.1	34.7
HR, 0.81 (95% CI 0367-1.00) P = 0.0377		



Clarke et al. 2023 ASCO GU. #LBA16.
Saad F, et al. *Lancet Oncol*. 2023;S1470-2045(23)00382-0.

MAGNITUDE: First-Line Niraparib + Abiraterone Acetate and Prednisone in mCRPC

- International, randomized, double-blind phase III trial (cutoff for final rPFS analysis: October 8, 2021)

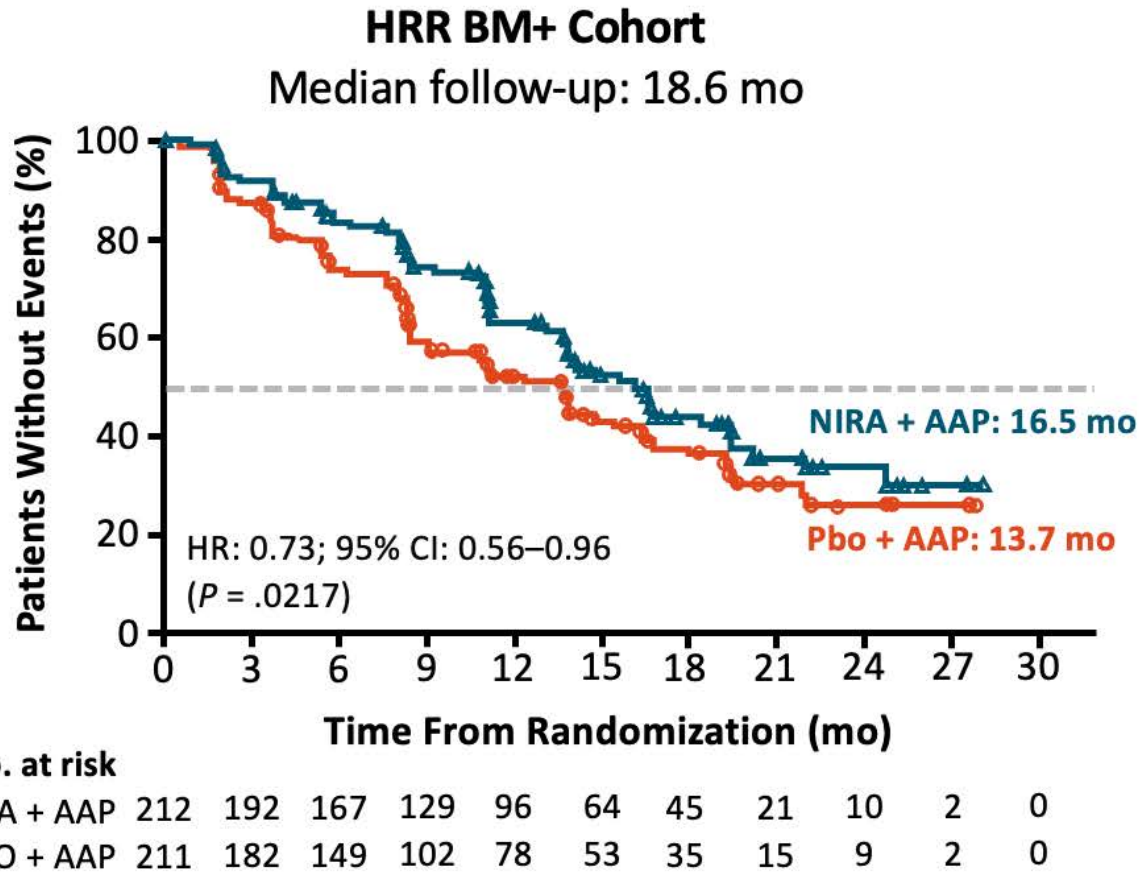


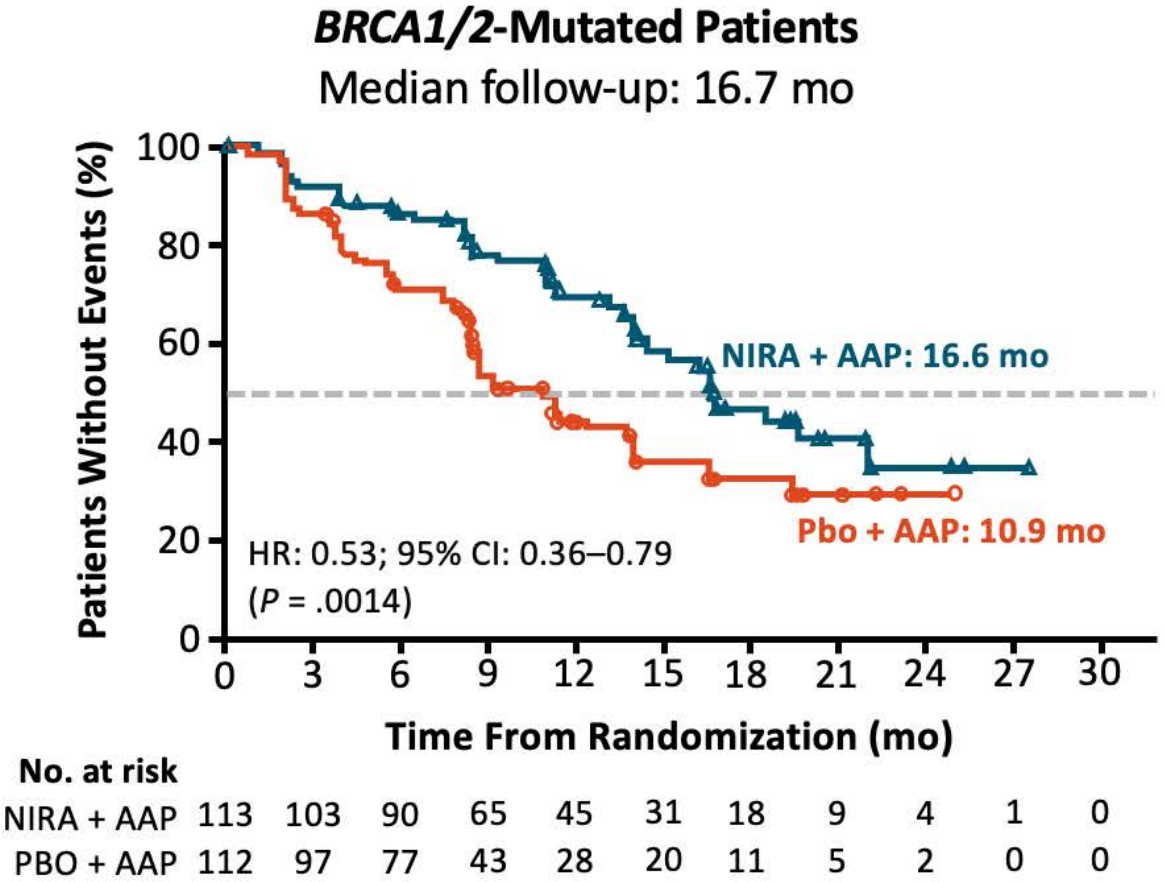
*HRR BM+ per tissue and/or plasma assays for *ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2*;
†AAP: abiraterone acetate 1000 mg PO QD + prednisone 10 mg PO QD.

- **Primary endpoint:** radiographic PFS by central review
- **Secondary endpoints:** OS, time to symptomatic progression, time to cytotoxic chemotherapy

Chi KN, et al. ASCO GU 2022. Abstract 12; Chi KN, et al. ASCO 2020. Abstract TPS5588. ClinicalTrials.gov ID: NCT03748641.

MAGNITUDE: Radiologic PFS by Central Review (primary endpoint)





Chi KN, et al. ASCO GU 2022. Abstract 12.

ASCO GU 2023 - MAGNITUDE: Second Interim Analysis

Endpoints at IA2	All HRR			*BRCA* subgroup		
	Median (mos) NIRA + AAP	Median (mos) PBO + AAP	HR (95% CI)	Median (mos) NIRA + AAP	Median (mos) PBO + AAP	HR (95% CI)
rPFS	16.7	13.7	0.76 (0.60, 0.97) P = 0.0280*	19.5	10.9	0.55 (0.39, 0.78) P = 0.0007*
TSP	NR	30.6	0.60 (0.42, 0.84) P = 0.0029^	NR	23.6	0.54 (0.35, 0.85) P = 0.0071*
TCC	NR	NR	0.67 (0.47, 0.94) P = 0.0206	NR	27.3	0.56 (0.35, 0.90) P = 0.0152*
OS primary stratified analysis	–	–	1.01 (0.75, 1.36) P = 0.948	–	–	0.88 (0.58, 1.34) P = 0.5505*
OS MVA	–	–	0.82 (0.60, 1.10) P = 0.1821*	–	–	0.68 (0.45, 1.05) P = 0.0793*

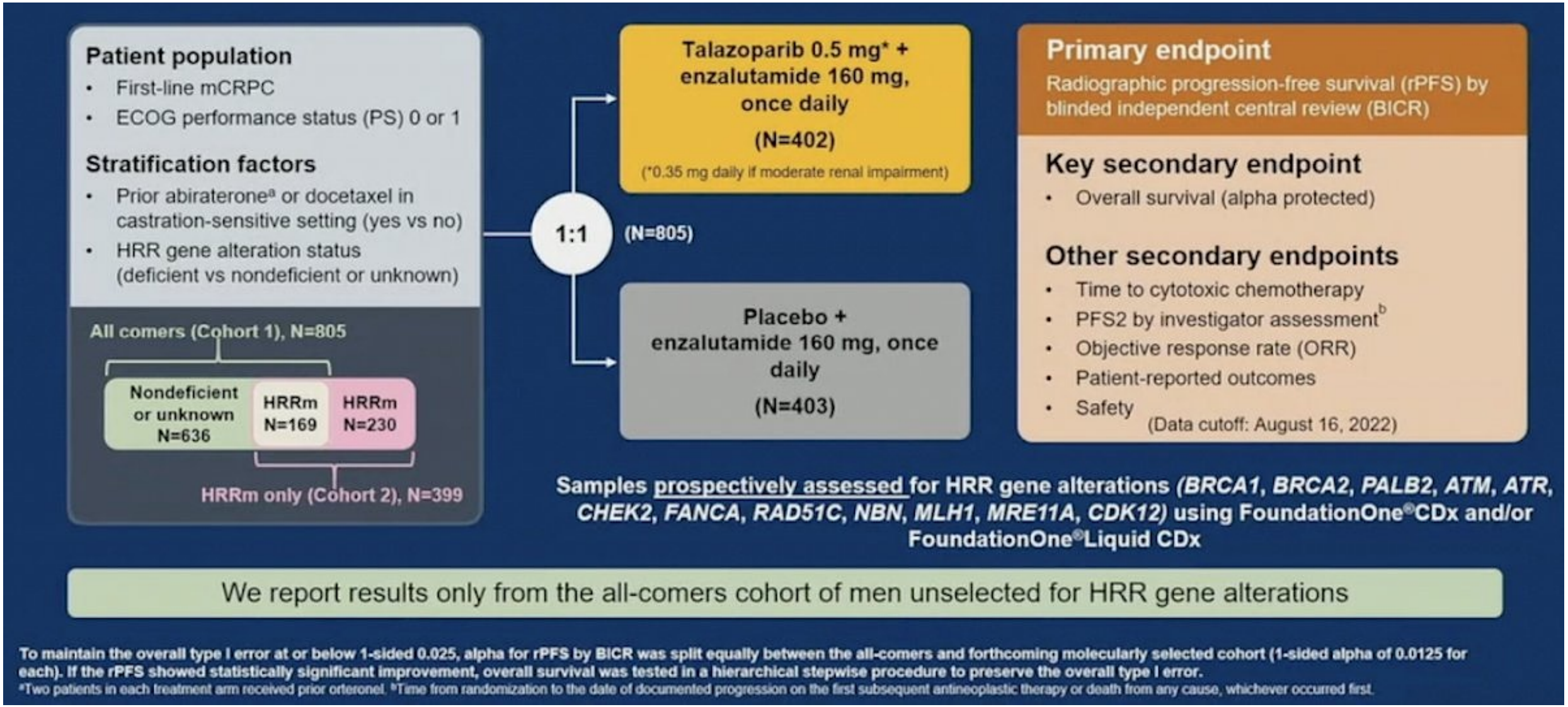
At 26.8 months of median follow-up

*Nominal p-value, ^Statistically significant.

Efstathiou E et al. ASCO GU 2023. Abstract #170.

Chi KN et al. *Ann Oncol*. 2023;34(9):772-782.

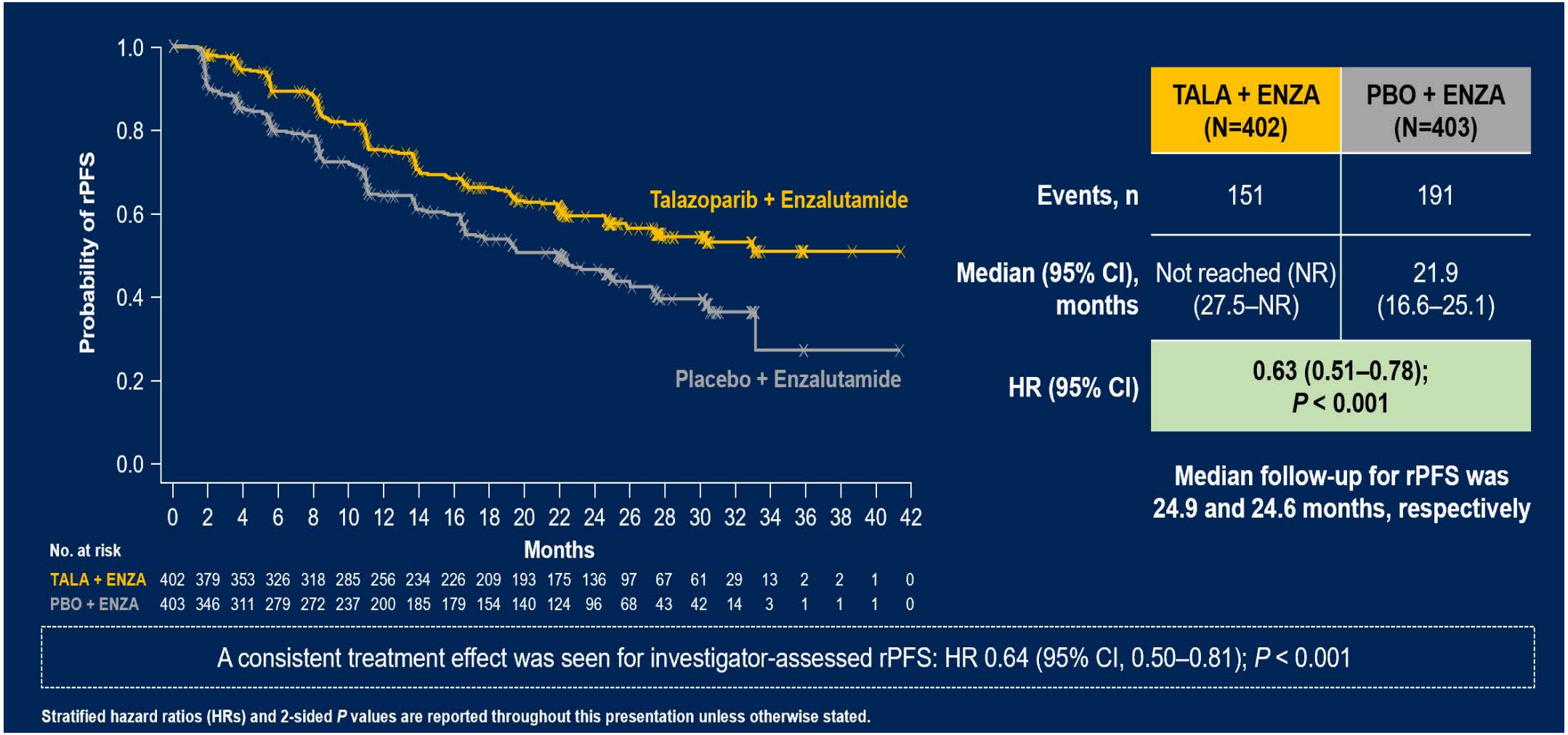
TALAPRO-2: Phase 3 Trial Design



Agarwal N et al. *Future Oncol*. 2022;18(4):425-436.

ASCO GU 2023 - TALAPRO-2: Primary Endpoint rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); *P* < 0.001	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

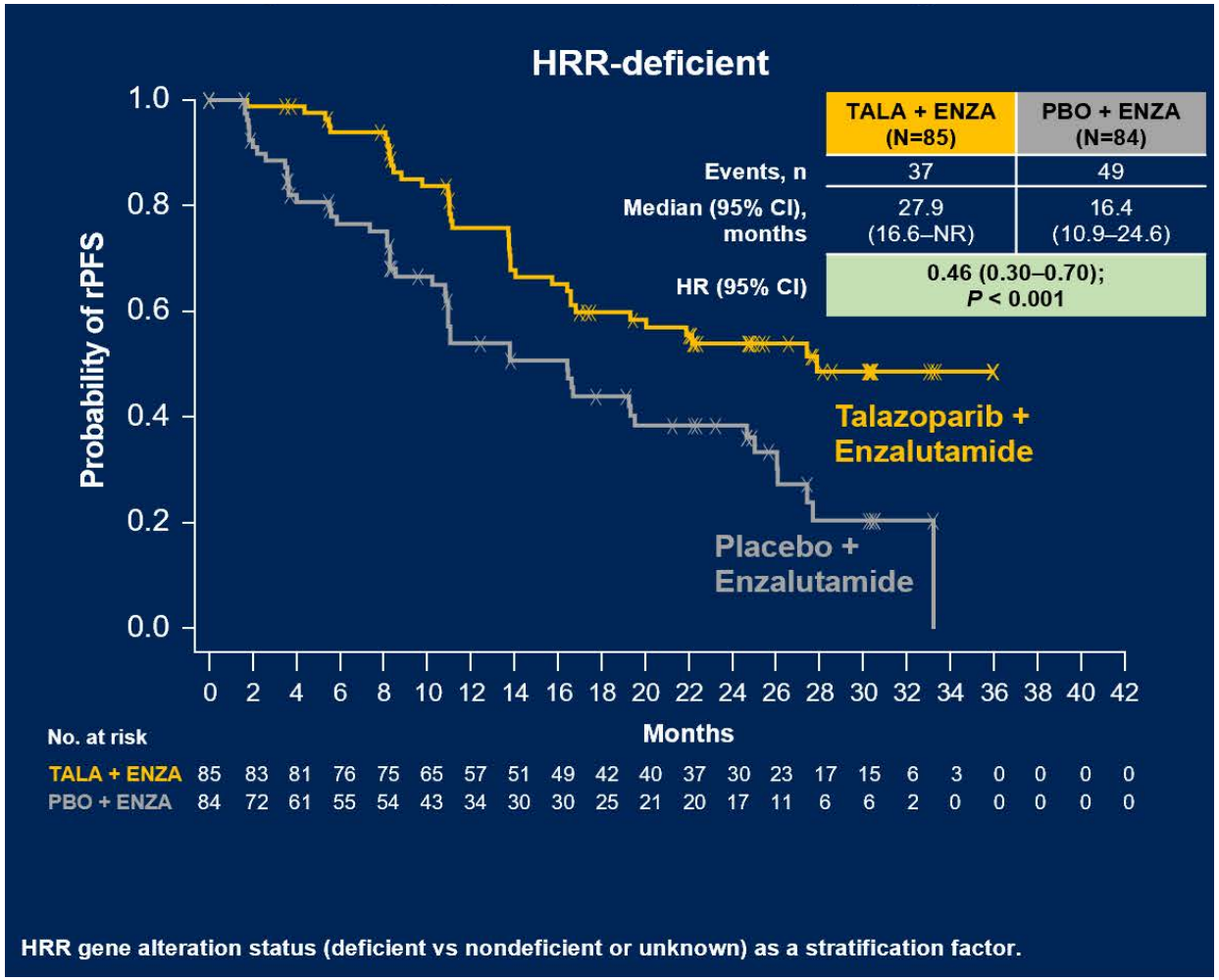
A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); *P* < 0.001

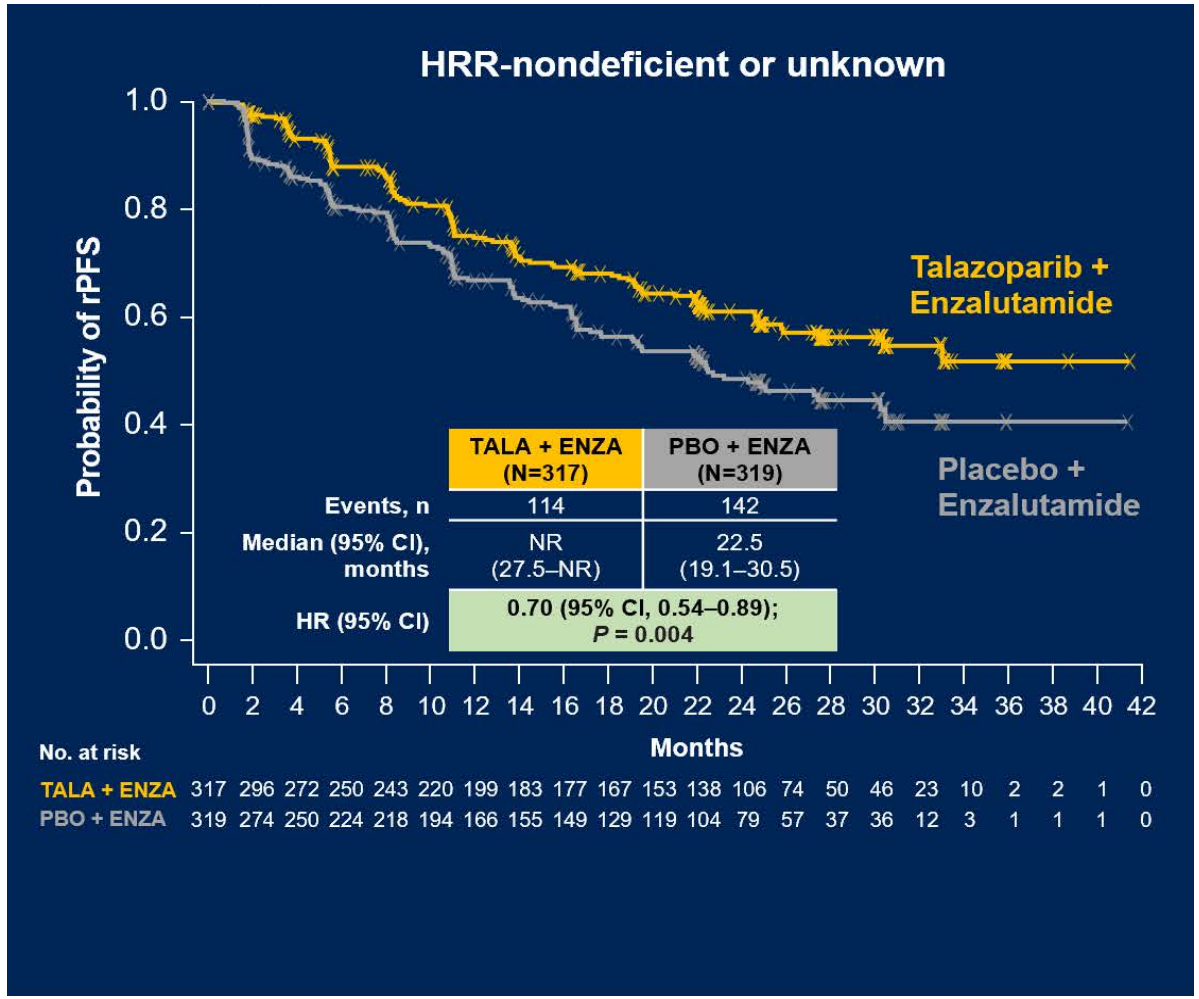
Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

Agarwal N et al. *Lancet*. 2023;402(10398):291-303. Agarwal N et al. ASCO GU 2023. Abstract LBA17.

ASCO GU 2023 – TALAPRO-2: rPFS by BICR by HRR Status

Clinically meaningful reduction in risk of progression or death regardless of HRR status





Agarwal N et al. *Lancet*. 2023;402(10398):291-303. Agarwal N et al. ASCO GU 2023. Abstract LBA17.

FDA Approval for PARPi + Abiraterone Combination for Prostate Cancer

Olaparib + Abiraterone acetate + prednisone

On May 31, 2023, on the basis of data from the PROpel study, the FDA approved olaparib with abiraterone and prednisone for the treatment of patients with deleterious or suspected deleterious BRCA-mutated mCRPC.

Talazoparib + enzalutamide

On June 20, 2023, on the basis of data from the TALAPRO-2 study, the FDA approved talazoparib with enzalutamide for the treatment of patients with homologous recombination repair gene-mutated mCRPC.

Niraparib + Abiraterone acetate + prednisone

On August 11, 2023, on the basis of data from the MAGNITUDE study, the FDA approved niraparib with abiraterone and prednisone for the treatment of patients with deleterious or suspected deleterious BRCA-mutated mCRPC.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-abiraterone-and-prednisone-or-prednisolone-brca-mutated-metastatic-castration
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-niraparib-and-abiraterone-acetate-plus-prednisone-brca-mutated-metastatic-castration

VISION: Phase 3 Study of ^{177}Lu-PSMA-617 in Patients with Progressive PSMA+ mCRPC

- International, prospective, open-label, multicenter, randomized phase 3 trial

N = 750

Key Eligibility Criteria

- Progressive mCRPC with a ^{68}Ga-PSMA-11 PET/CT positive scan (determined by central reader)
- Received at least 1 NAAD (enza or abi)
- Treated with at least 1 but no more than 2 previous taxane regimens
- ECOG PS 0-2

R
2:1

^{177}Lu-PSMA-617 7.4 GBq q6 wks x6
+
best supportive/standard of care

Best supportive/standard of care

Stratification factors:

- Serum LDH (≤ 260 IU/L vs >260IU/L)
- Presence of liver mets (Y/N)
- ECOG PS (0-1 vs 2)
- Inclusion of NAAD in best supportive/best std of care at time of randomization (Y/N)

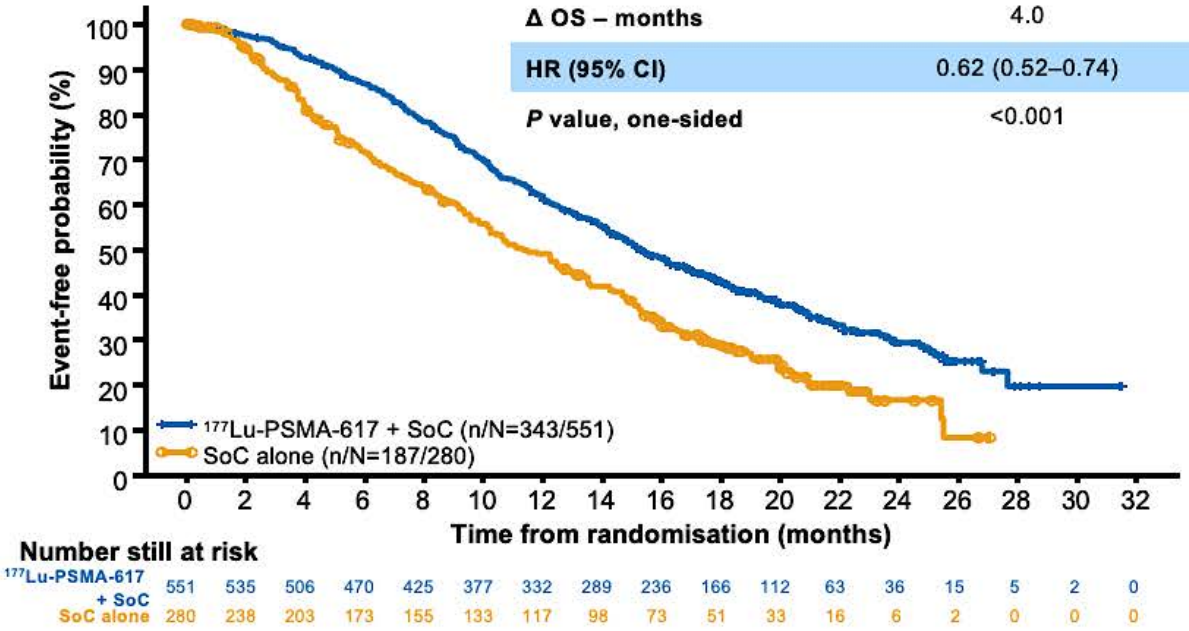
- Alternate Primary Endpoints: OS and rPFS
- Key Secondary Endpoints (with a control): RECIST response, time to first SSE
- Additional Secondary Endpoints: safety and tolerability, HRQoL, health economics, PFS, biochemical response

Sartor AO, et al. ASCO 2019. Abs TPS5099. ClinicalTrials.gov. NCT03511664

VISION: OS and rPFS Alternate Primary Endpoints

OS: 38% risk reduction for death
(OS analysis set)

	^{177}Lu-PSMA-617 + SoC (n=551)	SoC only (n=280)
Median OS – months	15.3	11.3
Δ OS – months	4.0	
HR (95% CI)	0.62 (0.52–0.74)	
P value, one-sided	<0.001	

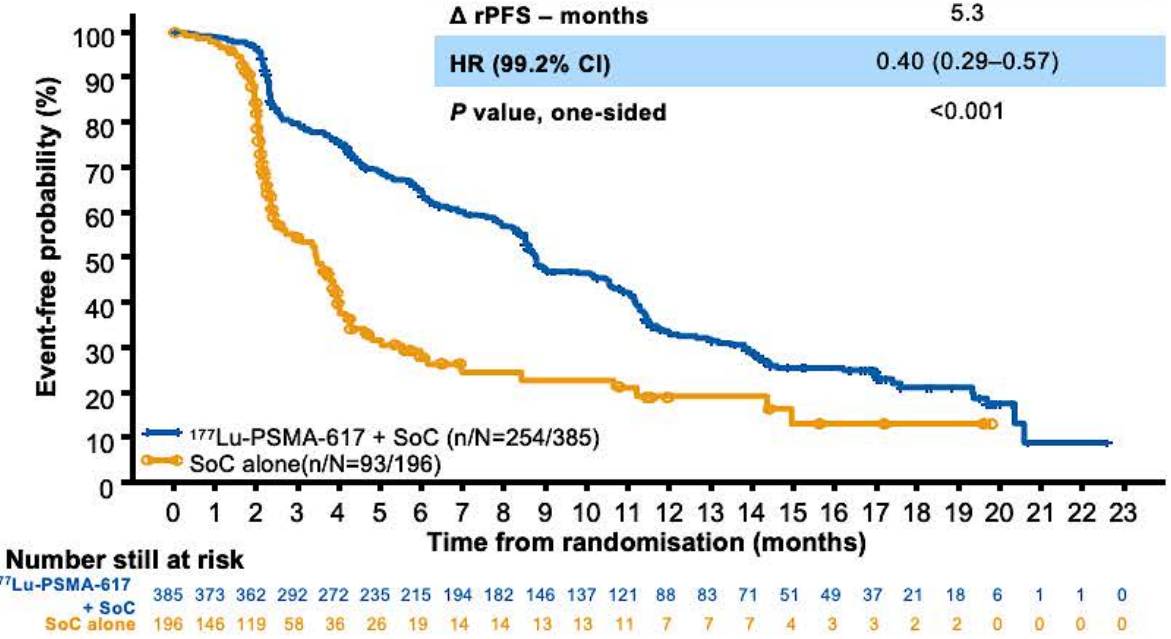


Number still at risk

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

rPFS: 60% risk reduction for progression/death
(rPFS analysis set)

	^{177}Lu-PSMA-617 + SoC (n=385)	SoC only (n=196)
Median rPFS[a] – months	8.7	3.4
Δ rPFS – months	5.3	
HR (99.2% CI)	0.40 (0.29–0.57)	
P value, one-sided	<0.001	



Number still at risk

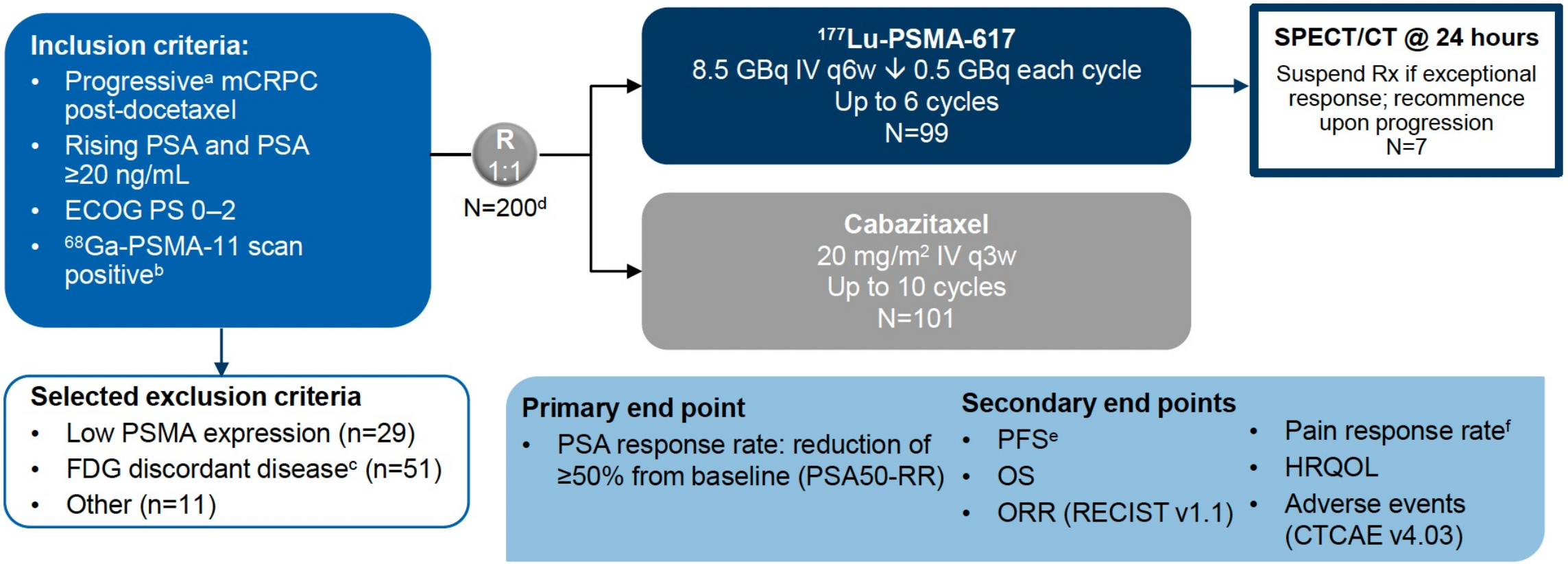
^{177}Lu-PSMA-617 + SoC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
SoC alone	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

Sartor AO, et al. New Engl J Med. 2021.

TheraP: Study Design

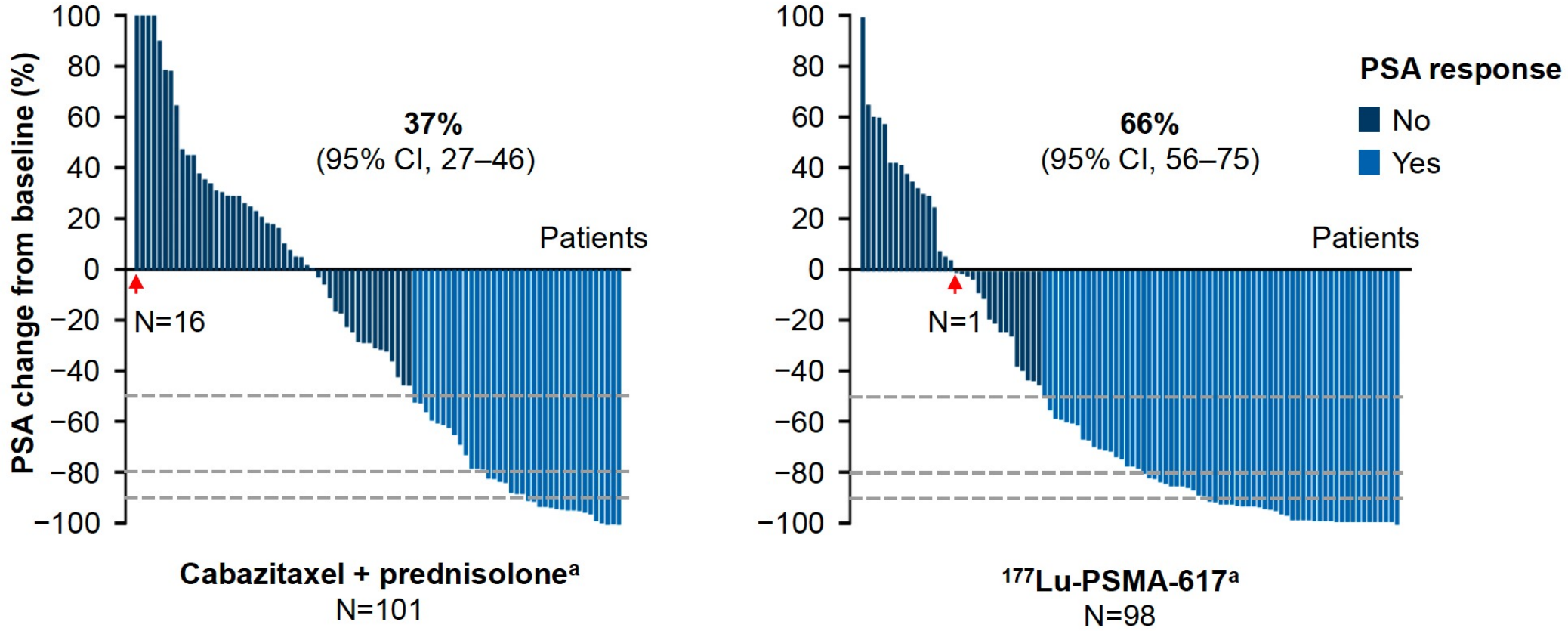
Multicenter, Unblinded, Randomized Phase II Trial in mCRPC

Aim: to compare the activity and safety of ^{177}Lu-PSMA-617 with cabazitaxel, in men for whom cabazitaxel was considered the next appropriate standard treatment



Hofman M, et al. Lancet. 2021.

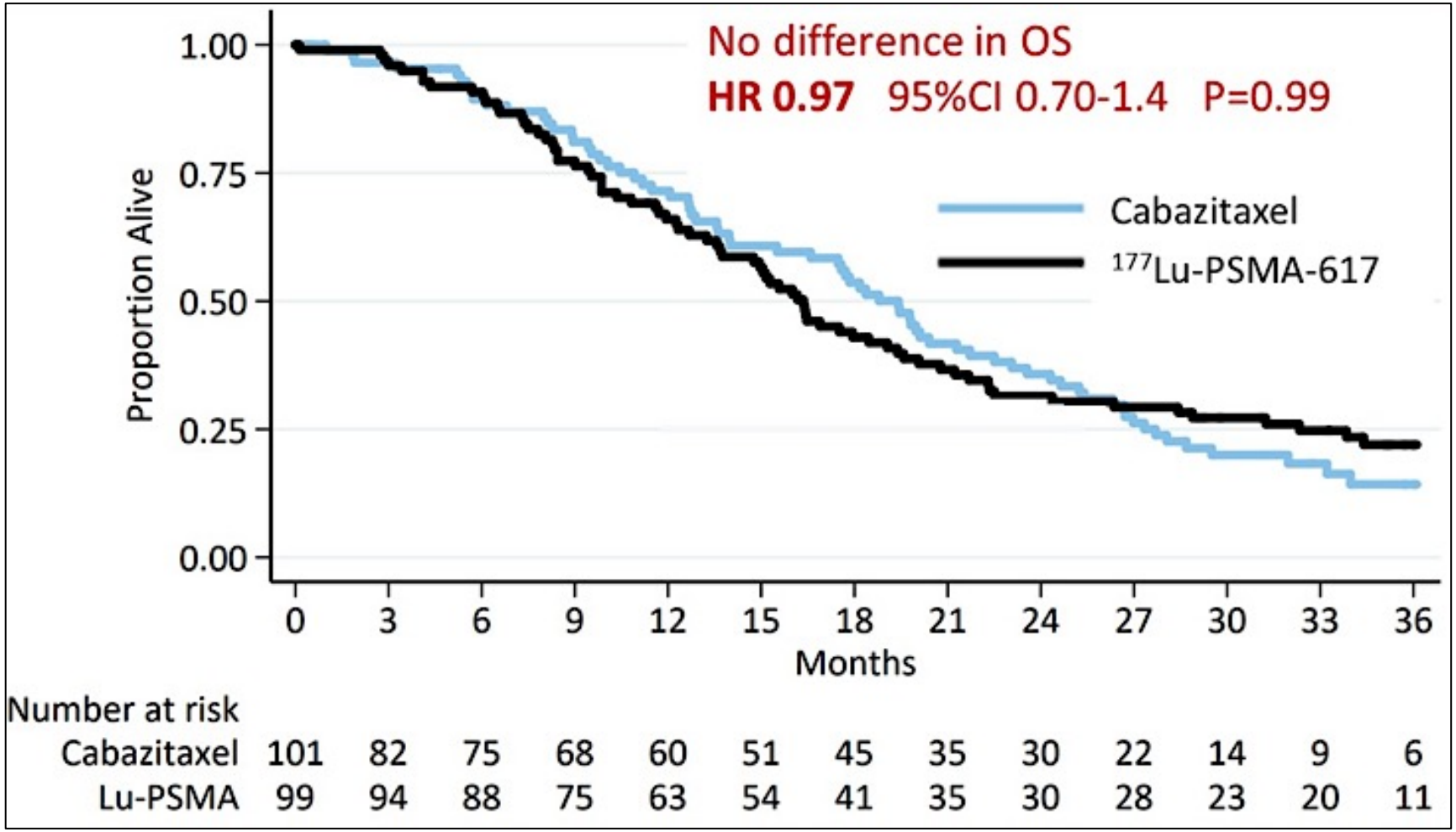
TheraP: Results – PSA ≥50% Response



Absolute difference in PSA50-RR between groups: 29% (*P*<0.0001)

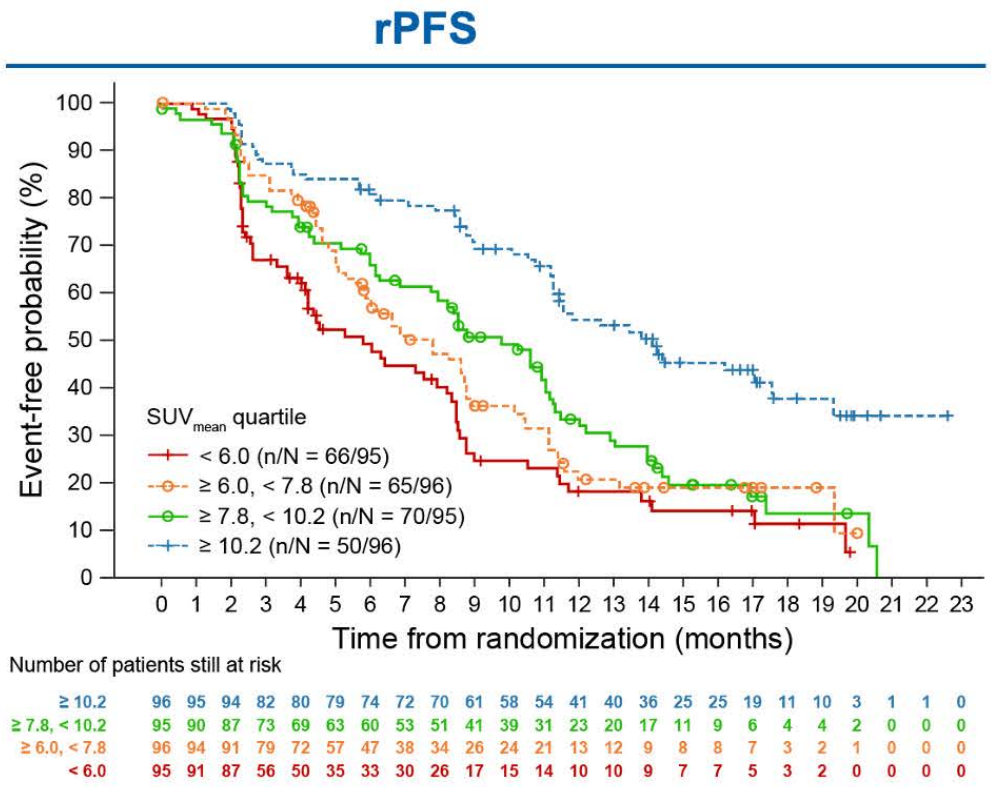
Hofman M, et al. Lancet. 2021.

Similar OS with ^{177}Lu-PSMA-617 vs cabazitaxel: 3-year follow-up of TheraP study



Hofman M, et al. ASCO 2022.

PSMA PET Expression as a Biomarker: Predicting Response to ^{177}Lu-PSMA-617 in VISION with SUV mean

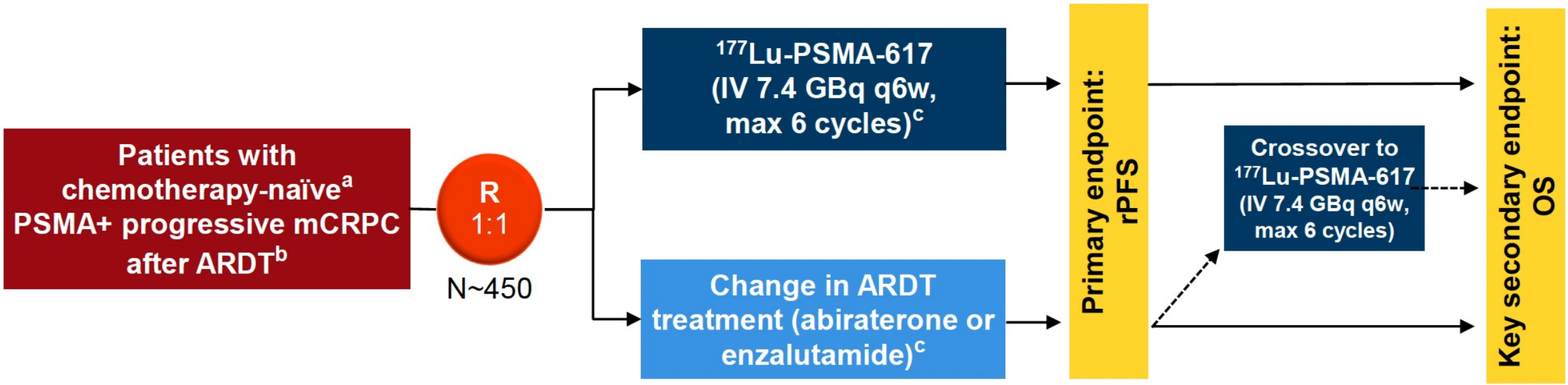


SUV_{mean} quartile	Median rPFS (months)
≥ 10.2 (highest)	14.1
≥ 7.8, < 10.2	9.8
≥ 6.0, < 7.8	7.8
< 6.0 (lowest)	5.8

- Patients with the highest whole-body SUV_{mean} had the greatest clinical benefit from ^{177}Lu-PSMA-617 + SoC
- However, favorable outcomes were observed regardless of SUV_{mean}

Kuo PH, et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5002). ASCO 2022.

PSMAfore Study Schema



Stratification factors

- Prior ARDT use in CRPC vs HSPC
- Presence of symptoms (asymptomatic/mildly symptomatic vs symptomatic)

Crossover

- Upon BICR-confirmed radiographic progression on ARDT, eligible patients meeting pre-defined criteria are permitted to crossover to receive ^{177}Lu-PSMA-617

ClinicalTrials.gov Identifier: NCT04689828

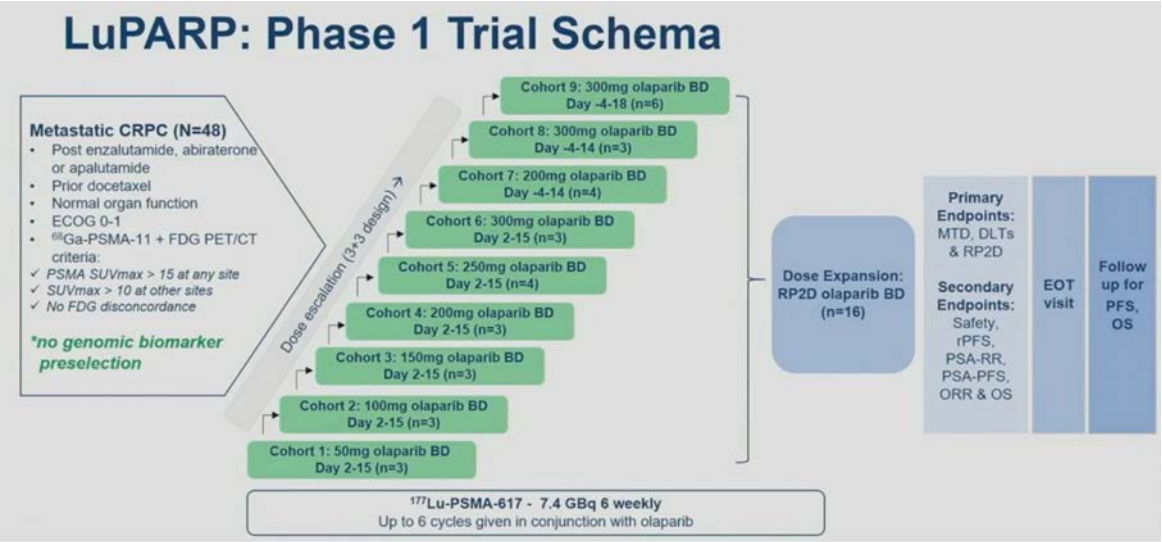
Lutetium Lu 177 vipivotide tetraxetan shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA-positive metastatic castration-resistant prostate cancer

Dec 05, 2022

https://www.novartis.com/news/media-releases/novartis-pluvictotm-shows-statistically-significant-and-clinically-meaningful-radiographic-progression-free-survival-benefit-patients-psma-positive-metastatic-castration-resistant-prostate-cancer

Phase 1: ^{177}Lutetium PSMA-617 Plus Olaparib

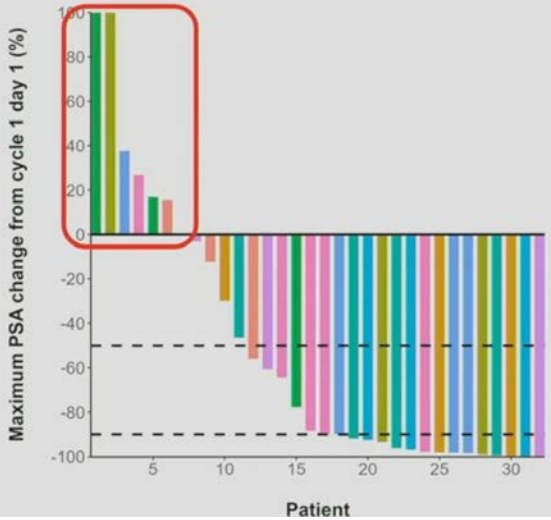
LuPARP: Phase 1 Trial Schema



LuPARP results: Treatment Related AEs >5%

	N=3 Cohort 1 ^{177}Lu-PSMA & 50mg olaparib BD Day 2-15			N=3 Cohort 2 ^{177}Lu-PSMA & 100mg olaparib BD Day 2-15			N=3 Cohort 3 ^{177}Lu-PSMA & 150 olaparib BD Day 2-15			N=3 Cohort 4 ^{177}Lu-PSMA & 200mg olaparib BD Day 2-15			N=4 Cohort 5 ^{177}Lu-PSMA & 250mg olaparib BD Day 2-15			N=3 Cohort 6 ^{177}Lu-PSMA & 300 olaparib BD Day 2-15			N=4 Cohort 7 ^{177}Lu-PSMA & 200mg olaparib BD Day -4-14			N=3 Cohort 8 ^{177}Lu-PSMA & 300mg olaparib BD Day -4-14			N=6 Cohort 9 ^{177}Lu-PSMA & 300mg olaparib BD Day -4-18			Total (n=32)		
No. cycles of treatment Median (range)	4 (4-5)			6 (5-6)			6 (2-6)			3 (2-4)			6 (4-6)			6 (5-6)			5.5 (3-6)			4 (3-6)			3 (2-5)			5 (2-6)					
Adverse Event (AE) Grade (G)	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3			
Anemia	1	-	-	2	1	-	-	-	-	-	-	-	1	1	1	-	-	1	1	-	-	-	-	-	-	1	-	5	3	2			
Neutropenia	-	-	-	1	-	-	-	-	-	-	-	-	-	-	1*	-	-	1	-	-	-	-	-	-	-	-	-	1	-	2			
Thrombocytopenia	-	1	-	1	-	-	1	-	-	1	-	-	1	-	1	-	1	-	-	-	-	-	-	-	1	-	-	5	2	1			
Nausea	1	2	-	3	-	-	1	1	-	2	-	-	1	1	-	1	1	-	2	1	-	-	-	-	2	-	-	13	6	-			
Dry Mouth	3	-	-	3	-	-	3	-	-	2	-	-	3	1	-	2	1	-	1	1	-	2	-	-	3	-	-	22	3	-			
Constipation	-	-	-	-	-	-	-	1	-	2	-	-	-	-	-	1	-	-	1	1	-	1	-	-	2	-	-	7	2	-			
Vomiting	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	1	-	-	1	-	-	3	1	-			
Gastroesophageal Reflux	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	1	-	-	2	1	-			
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	3	-	-			
Weight Loss	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	1	1	-			
Anorexia	1	-	-	2	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-	6	-	-			
Dry Eye	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	-	2	-	-			
Fatigue	-	-	-	1	-	-	1	-	-	2	-	-	1	-	-	2	-	-	1	-	-	1	-	-	6	-	-	15	-	-			

LuPARP results: PSA Response



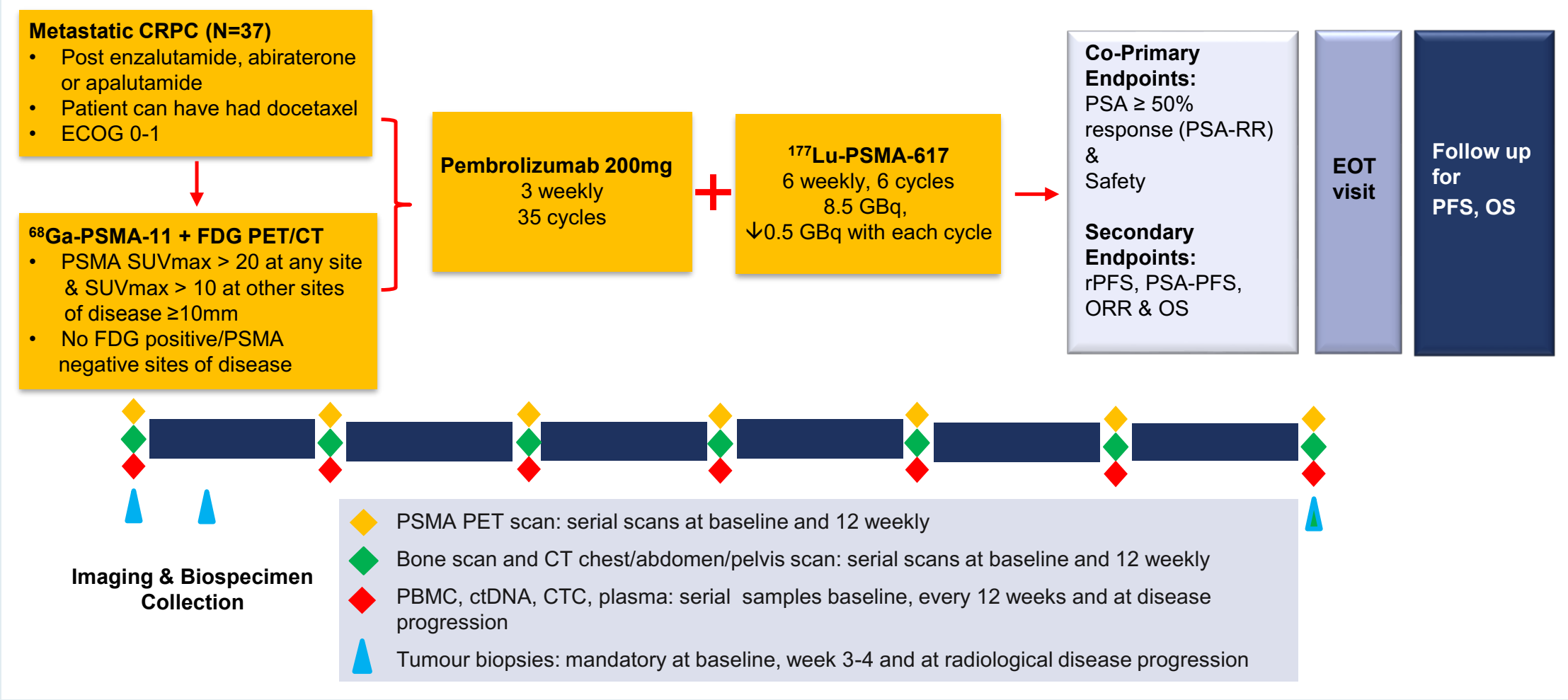
Cohort 1: 50mg Day 2-15
Cohort 2: 100mg Day 2-15
Cohort 3: 150mg Day 2-15
Cohort 4: 200mg Day 2-15
Cohort 5: 250mg Day 2-15
Cohort 6: 300mg Day 2-15
Cohort 7: 200mg Day -4-14
Cohort 8: 300mg Day -4-14
Cohort 9: 300mg Day -4-18

	LuPARP	TheraP	VISION
PSMA SUVmax	>15	>20	> Liver
PSA50 response	66% (21/32)	66% (67/99)	46% (177/385)
PSA80 response	53% (17/32)	48% (48/99)	33% (127/385)
PSA90 response	44% (14/32)	38/99 (38%)	N/A
ORR by RECIST 1.1	78% (7/9)	49% (48/99)	30% (95/319)

1. Sartor O et al. N Engl J Med 2021;385(12):1091-1103.
2. Hofman MS et al. Lancet 2021;397(10276):797-804

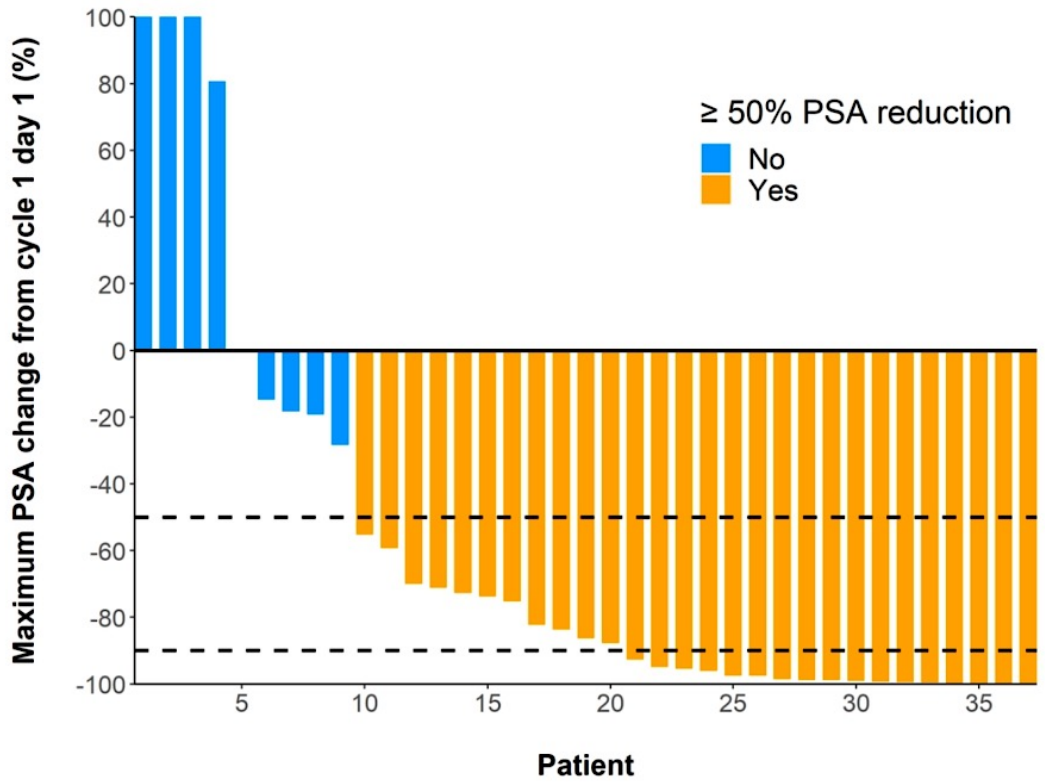
Sandhu S, et al. ASCO Annual Meeting 2023.

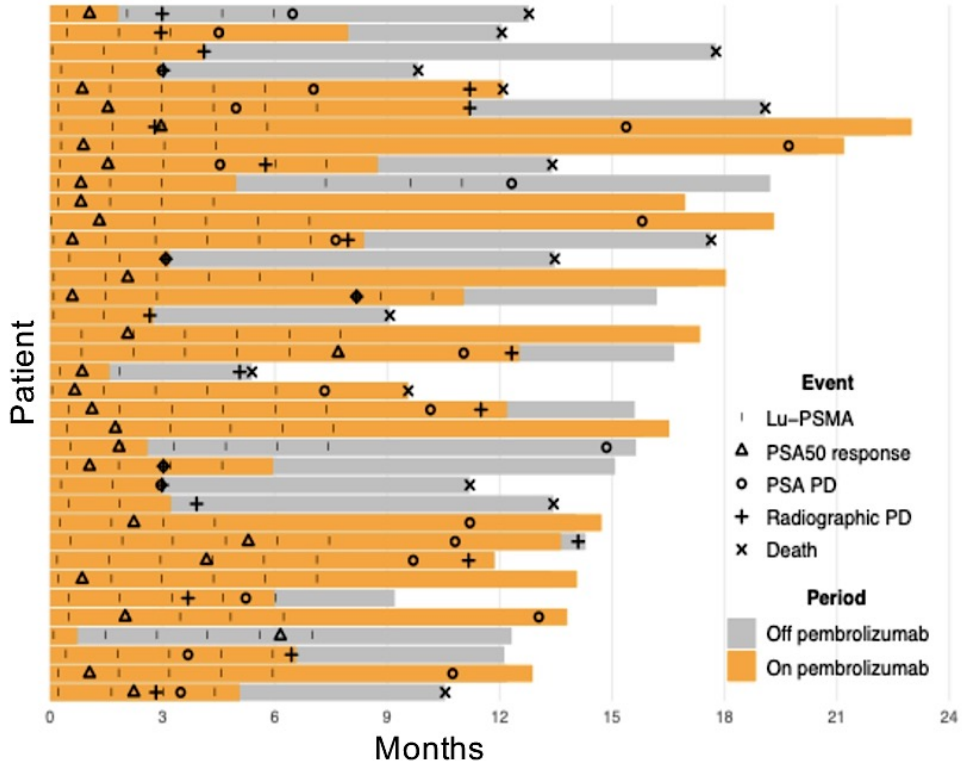
PRINCE: Phase Ib Study of Pembrolizumab with ^{177}Lu-PSMA-617 for mCRPC



Sandhu S et al. ESMO 2021;Abstract 577O.

PRINCE: Updated PSA Response Rate (Primary Endpoint)





PSA ≥ 50% response = 76% (28/37 95% CI:59-88)
ORR by RECIST 1.1 = 78% (7/9)

median follow up: 16 months at data cut off

Sandhu S et al. ASCO 2022;Abstract 5017.

CONTACT-02

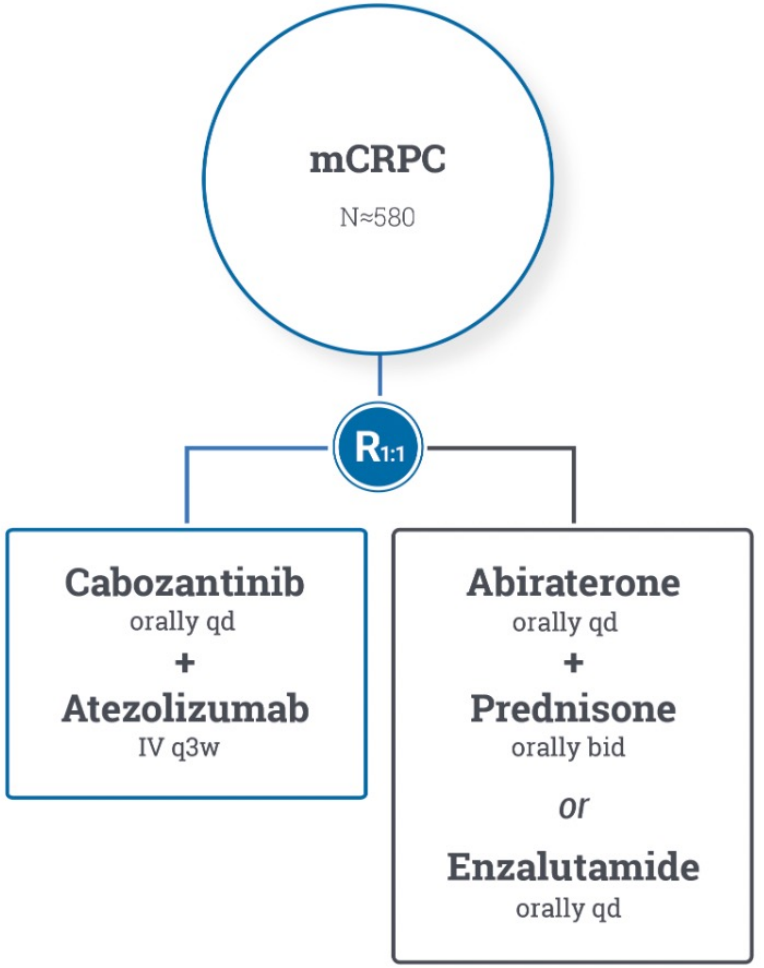
> STUDY OVERVIEW

Positive Results Announced from Phase 3 CONTACT-02 Pivotal Trial Evaluating Cabozantinib in Combination with Atezolizumab in Metastatic Castration-Resistant Prostate Cancer

Corporate - 21 August 2023 - 15 mins read

– Cabozantinib in combination with atezolizumab demonstrated a statistically significant reduction in the risk of disease progression or death compared with a second novel hormonal therapy in patients with metastatic castration-resistant prostate cancer

– A trend toward improvement in overall survival was observed at first interim analysis



Conclusions

- Treatment of men with mCRPC continues to evolve rapidly.
- PARPi monotherapy is an option for patients with HRR alterations, and may be superior to chemotherapy in BRCAm patients.
- PSMA PET scans can identify patients who are eligible for ^{177}lutetium PSMA-617 after ARPIs and docetaxel
  - Data describing the benefit of ^{177}lutetium PSMA-617 before chemo are imminent
- Combinations of PARP inhibitors with ARSIs are newly approved
- Novel approaches including cabozantinib plus atezolizumab are on the horizon for treatment of mCRPC.

Clinical Questions and Cases

Case Presentation: 64-year-old man with BRCA1/2 wild-type mCRPC s/p enzalutamide, docetaxel and cabazitaxel

Dr Lowell Hart (Fort Myers, Florida; 10-12-2020)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 63-year-old man with BRCA1/2 wild-type mCRPC s/p abiraterone, enzalutamide and docetaxel; radium-223?

Dr Sunil Gandhi (Lecanto, Florida; 4-28-2021)

RTP
RESEARCH
TO PRACTICE

Prostate Cancer
Lutetium Lu 177 Vipivotide Tetraxetan

- **Procedures**
- **PSMAfore trial (press release and upcoming ESMO Presidential presentation)**
- **Risks and benefits/sequencing**

Discussion Question

A 75-year-old man who is receiving ADT and enzalutamide for mHSPC experiences disease progression. Genetic testing is negative for HRR mutations. Regulatory and reimbursements issues aside, what systemic treatment would you most likely recommend?

Discussion Question

What adverse event was most commonly observed with lutetium Lu 177 vipivotide tetraxetan in the Phase III VISION study?

Case Presentation: A 67-year-old man with mCRPC and a germline BRCA2 mutation who receives later-line olaparib for CRPC

Dr Zanetta Lamar (Naples, Florida; 10-14-2020)

RTP
RESEARCH
TO PRACTICE

Prostate Cancer
PARP Inhibitors (Metastatic Disease)

- Germline and somatic evaluation
- PARP inhibitor monotherapy and combinations
- BRCA and other germline mutations: Genetic counseling

Discussion Question

Which PARP inhibitor-based combinations demonstrated improved radiographic progression-free survival for patients with HRR-proficient mCRPC?

Discussion Question

A 75-year-old man with prostate cancer metastatic to the bone and lungs and a BRCA2 germline mutation receives ADT and docetaxel and experiences disease progression 18 months later. He responds to enzalutamide and ADT, then experiences minimally symptomatic disease progression. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

Prostate Cancer Immunotherapy?

- **Cabozantinib/atezolizumab in mCRPC — CONTACT-02 (press release)**

Current Approaches and Future Strategies in Oncology: A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists and Research Institute

A CME/MOC- and NCPD-Accredited Event

Saturday, October 7, 2023
7:15 AM – 12:30 PM ET

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We are taking a short break!

The program will resume at 9:30 AM ET

Up Next…

Drs Gregory Riely and Heather Wakelee discuss the management of non-small cell lung cancer

Please complete Part 2 of the premeeting survey

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