Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

Welcome FCS Members!

RTP
RESEARCH
TO PRACTICE

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.

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

RTP RESEARCH TO PRACTICE

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 surveys.

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

Get CME/ACPE/NCPD Credit: A credit link will be provided in the chat room at the conclusion of the program.

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

Join Us In Person or Virtually

Cases from the Community: Integrating New Research Findings into Practice

A Multitumor Educational Symposium in Partnership with the American Oncology Network

Saturday, November 16, 2024

Lung Cancer Update: Antibody-Drug Conjugates and New Approaches

Faculty

Edward B Garon, MD, MS

Leukemia and Myelodysplastic Syndromes

Faculty

Harry Paul Erba, MD, PhD

Moderator

Stephen "Fred" Divers, MD

RTP RESEARCH TO PRACTICE

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Myelofibrosis

Faculty

Faculty to be announced.

Gynecologic Cancers

Faculty

Kathleen N Moore, MD, MS

Moderator

Stephen "Fred" Divers, MD

RTP RESEARCH TO PRACTICE

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A Multitumor Educational Symposium in Partnership with the American Oncology Network

Saturday, November 16, 2024

Hepatobiliary Cancers

Faculty

Daneng Li, MD

Colorectal and Gastroesophageal Cancers

Faculty

Christopher Lieu, MD

Moderator

Stephen "Fred" Divers, MD

RTP RESEARCH TO PRACTICE

Exploring the Current Management Paradigm for Patients with Metastatic Triple-Negative Breast Cancer

A CME/MOC-Accredited Live Webinar

In Partnership with Florida Cancer Specialists & Research Institute

Monday, November 18, 2024
5:00 PM – 6:00 PM ET

Faculty

Priyanka Sharma, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Metastatic Triple-Negative Breast Cancer Survey for Florida Cancer Specialists Members

Dear Dr ,

On behalf of Dr Neil Love and Research To Practice, I am pleased to extend an invitation to participate in a survey focused on your usual treatment approaches for metastatic triple-negative breast cancer (mTNBC). We are conducting this survey in conjunction with a webinar we are hosting in November. Note, if you have already received this email, and not completed the survey, it has been slightly revised.

For this survey, we will ask for de-identified information on a minimum of 2 and up to 4 patients from your practice with mTNBC whom you have treated within the past 18 months. Additionally, we will ask that you provide 1 question to the faculty related to each case. You will also have the opportunity to weigh in on your preferred treatment options for a number of mTNBC scenarios.

The survey will take approximately **30 minutes** to complete, and you will receive a **$400 honorarium** for your participation and providing 2 cases, and up to $500 for providing information related to 4 cases from your practice. If you would like to participate, we ask that you please complete the survey no later than **Friday, November 8, 2024**.

To get started, click the link below:

CLINICAL SURVEY

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Hematologic Cancers

A CME Friday Satellite Symposium and Webcast Series
Preceding the 66th ASH Annual Meeting and Exposition

Friday, December 6, 2024

Chronic Myeloid Leukemia
7:30 AM – 9:00 AM PT

Chronic Lymphocytic Leukemia
7:30 AM – 9:30 AM PT

CAR T-Cell Therapy and Bispecific Antibodies in Lymphoma
11:30 AM – 1:30 PM PT

Myelofibrosis
11:30 AM – 1:30 PM PT

Acute Myeloid Leukemia
3:15 PM – 5:15 PM PT

Multiple Myeloma
3:15 PM – 5:15 PM PT

RTP RESEARCH TO PRACTICE

Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Breast Cancer

A 3-Part CME Hybrid Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

HER2-Low and HER2-Ultralow Breast Cancer

Tuesday, December 10, 2024

7:15 PM – 8:45 PM CT

New Developments in Endocrine Treatment for Breast Cancer

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT

Management of Metastatic Breast Cancer

Thursday, December 12, 2024

7:15 PM – 9:15 PM CT

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Save The Date

Fourth Annual
National General Medical Oncology Summit

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

Friday to Sunday, February 28 to March 2, 2025

Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Agenda

Module 1 — HR-Positive Breast Cancer: *Drs O'Shaughnessy and Wander*

Module 2 — Prostate Cancer: *Drs M Smith and Srinivas*

Module 3 — Lung Cancer: *Drs Goldberg and Sabari*

Module 4 — Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia: *Drs Kahl and S Smith*

Module 5 — Multiple Myeloma: *Drs Lonial and Raje*

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Module 5 — Multiple Myeloma: *Drs Lonial and Raje*

HR-Positive Breast Cancer Faculty

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Chair, Breast Disease Committee
Sarah Cannon Research Institute
Dallas, Texas

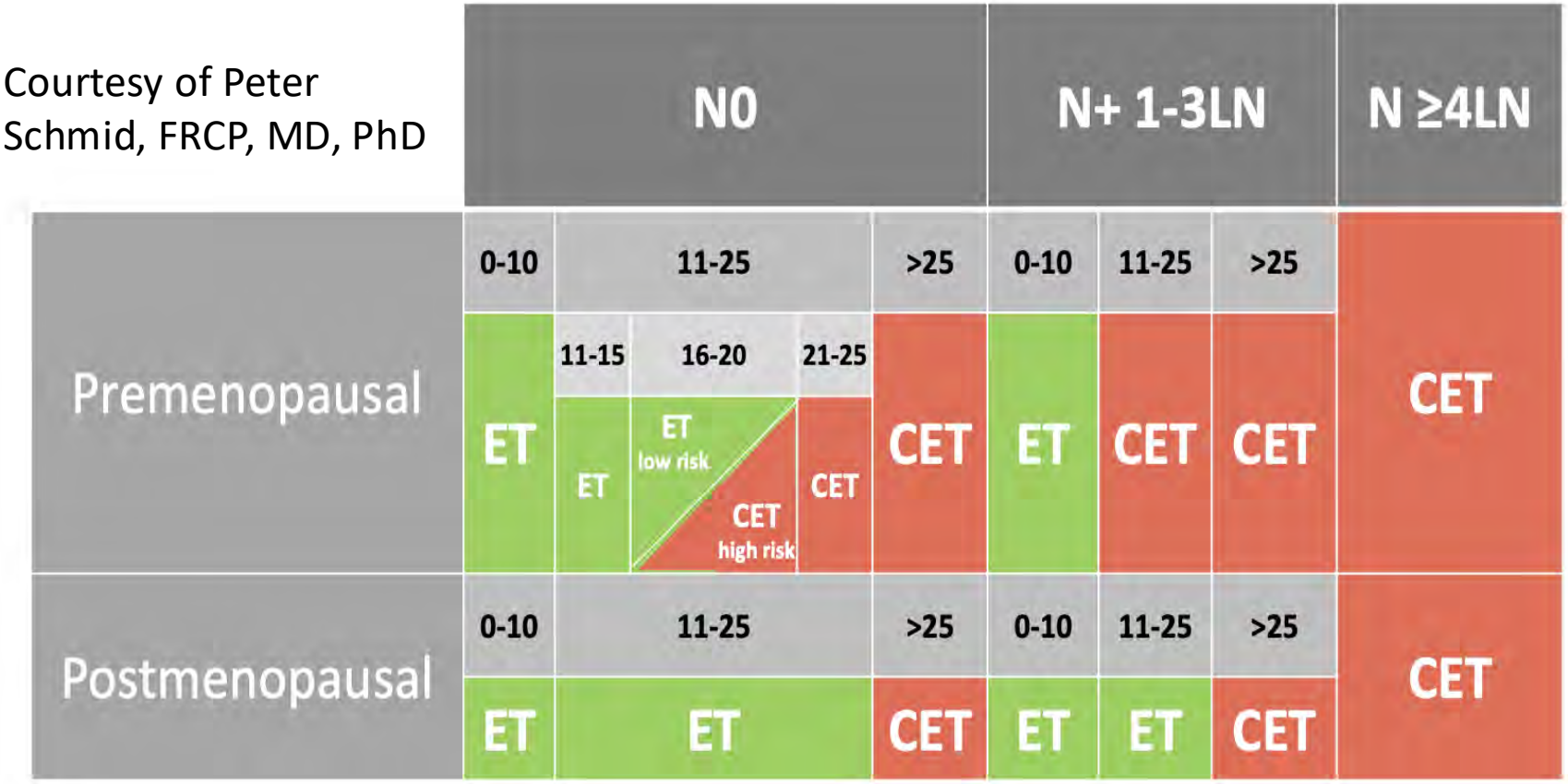
Seth Wander, MD, PhD
Assistant Professor of Medicine
Harvard Medical School
Attending Physician
Massachusetts General Hospital
Boston, Massachusetts

Module 1
Hormone Receptor-Positive Breast Cancer

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Texas Oncology
Sarah Cannon Research Institute
Dallas TX

Which HR+ HER2- EBC Patients Benefit from Chemotherapy?

Courtesy of Peter Schmid, FRCP, MD, PhD



70-gene Signature

Clinical High Risk +
Genomic Low Risk
0-3+ nodes

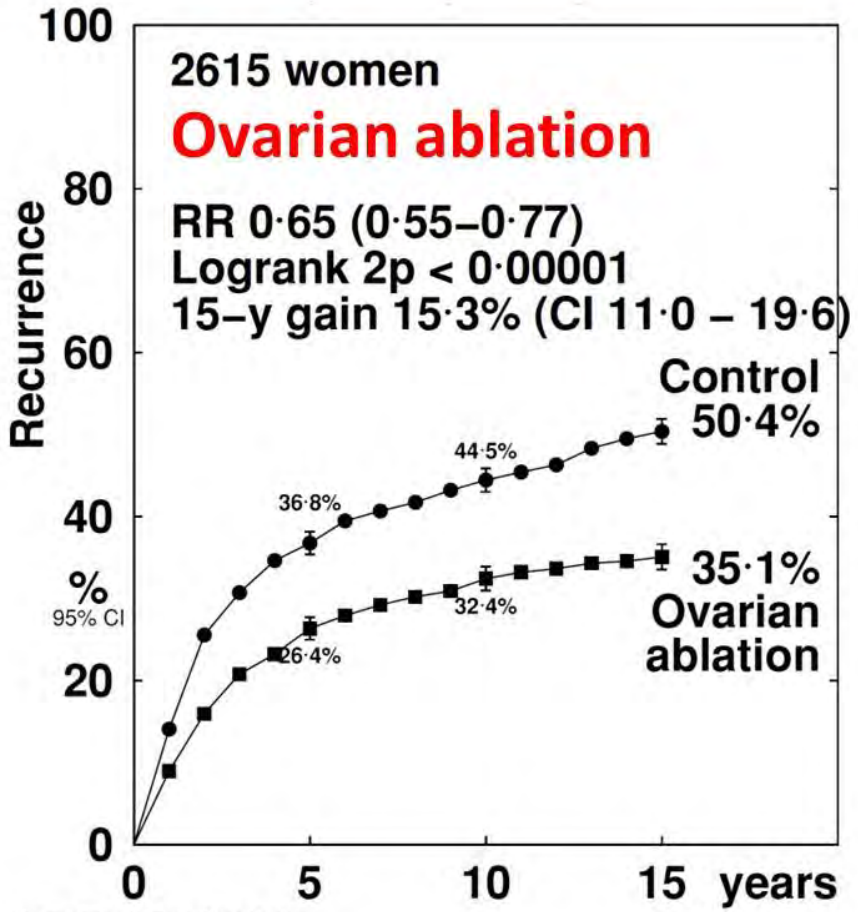
Postmenopausal ET
Premenopausal CET

< 20% premen HR+ pts TAILORx, RxPONDER and MINDACT had LHRH agonist

NCCN

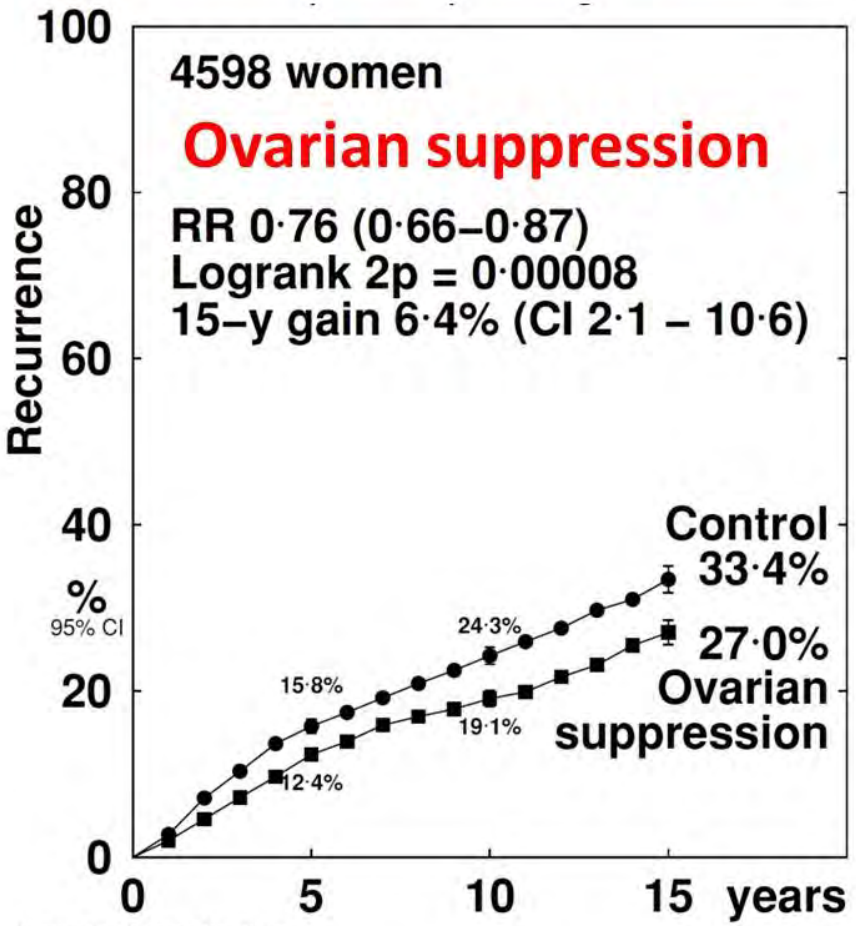
T1aN0: ER+ and HER2+/-: Endocrine therapy only and ER- HER2+ and TN no chemoRx
T1bN0: Consider chemoRx (+ trastuzumab and ET as appropriate)

Ovarian ablation/suppression vs not: Recurrence by method
(B) 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.	7·42 (410 / 5529)	1·93 (79 / 4091)	1·13 (30 / 2645)	1·29 (68 / 5267)
Control	8·78 (404 / 4603)	2·50 (82 / 3284)	2·08 (39 / 1879)	1·39 (51 / 3678)
Rate ratio, from	0·65 CI 0·53 – 0·80	0·66 CI 0·43 – 1·01	0·40 CI 0·20 – 0·78	0·85 CI 0·50 – 1·44
(O–E) / V	–40·3 / 94·3	–8·6 / 20·8	–7·8 / 8·5	–2·3 / 13·9



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	2·65 (257 / 9703)	1·69 (99 / 5841)	1·81 (48 / 2646)	1·58 (4 / 253)
Control	3·41 (336 / 9841)	2·06 (116 / 5632)	2·55 (61 / 2393)	1·40 (3 / 215)
Rate ratio, from	0·75 CI 0·63 – 0·89	0·77 CI 0·58 – 1·02	0·75 CI 0·50 – 1·11	1·49 CI 0·31 – 7·13
(O–E) / V	–37·5 / 132·0	–13·0 / 49·1	–7·0 / 24·1	0·6 / 1·6

Gray R, et al. EBCTCG, ASCO 2023

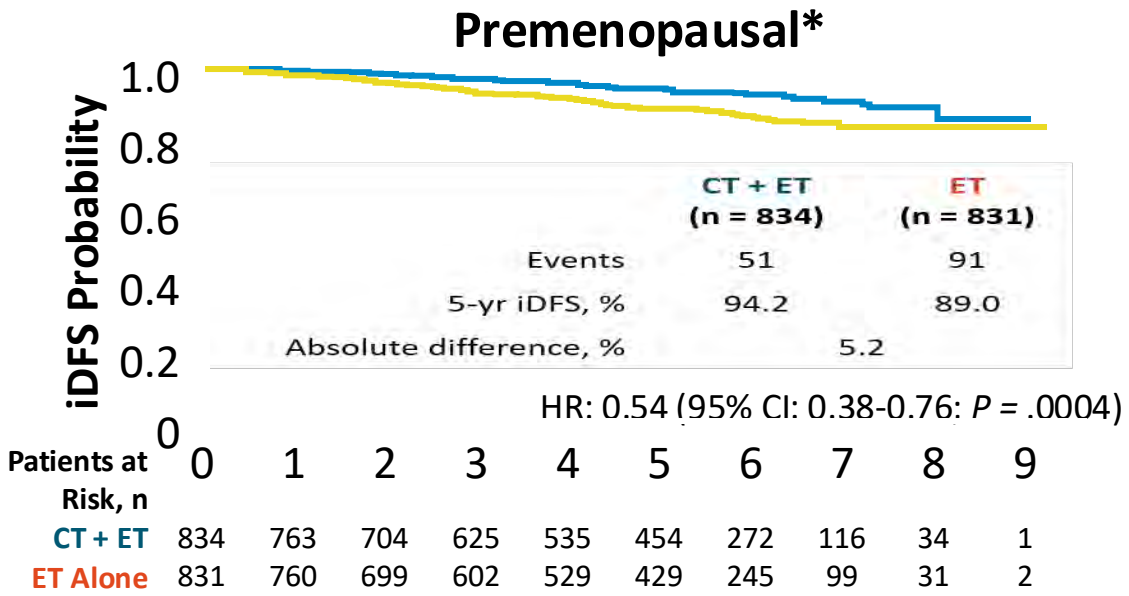
RxPONDER Subset Analysis: iDFS by Menopausal Status

N=5015

Chemotherapy Followed by ET
(n = 2509)

ET Alone
(n = 2506)

Premenopausal, HR+ HER2- EBC, 1-3 LN+ (SLND or ALND), Oncotype RS <25, candidate for chemo



- **No significant iDFS difference for postmenopausal women**
- **Assessed benefit chemotherapy in pts <55 yrs of age using serum markers of ovarian function/reserve**
- **Less iDFS benefit in "premenopausal" women ≥50 to 55 yrs of age**
- **Low serum anti-Müllerian hormone and inhibin B are markers of diminished ovarian reserve and lack of benefit from adjuvant chemotherapy**

Kalinsky K et al. ASCO 2024;Abstract 505.

BR009: Schema

- Premenopausal; HR+/HER2- BC
- pN0 with RS 16-20 (high clinical risk) or RS 21-25
- pN1 with RS 0-25

Stratification

- Nodal Status (pN0 vs. pN1)
- RS (0-15 vs. 16-25)

Randomization

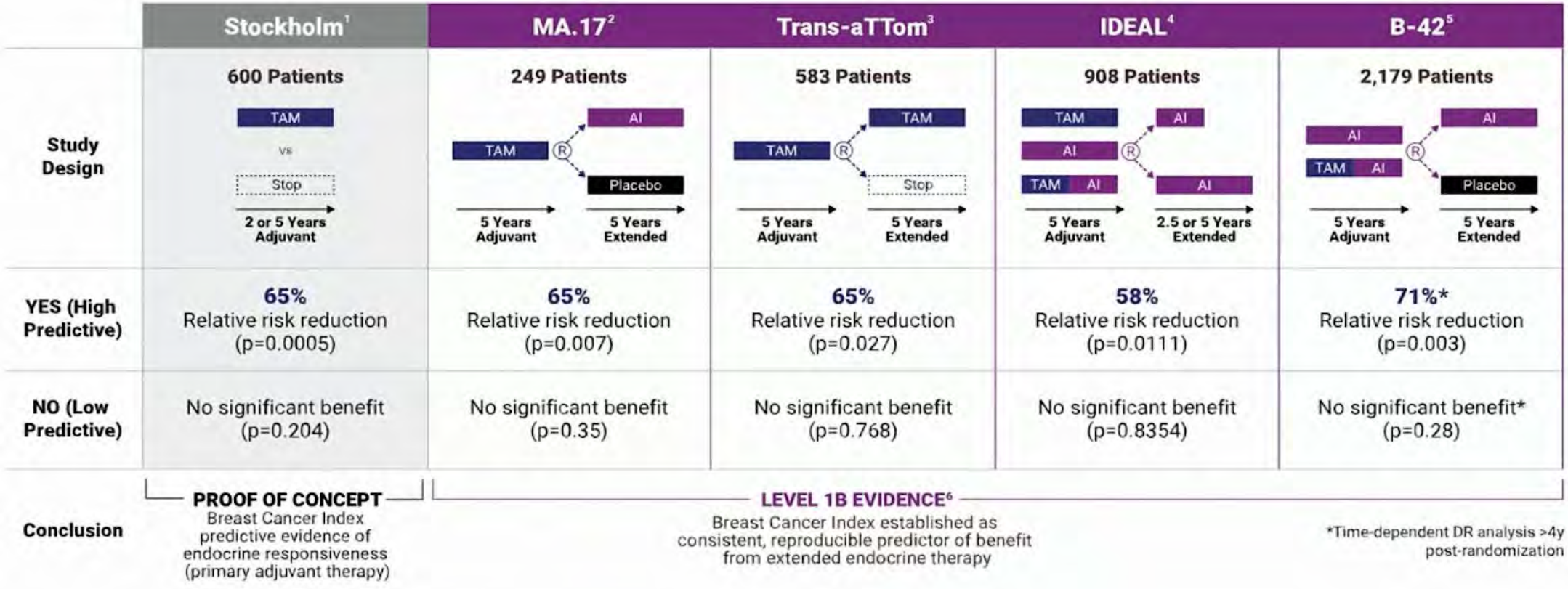
N=3,960

Chemotherapy + Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years	Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years

* Tamoxifen can be used if AI is not tolerated

BCI: predicting benefit from extended ET

H/I – Measure of ET-sensitivity; how driven by ER BC is



- **In patients with node negative or 1-3 LN+, can consider using Breast Cancer Index or other tests (e.g., CTS5 Dowsett, JCO 2018; https://cts5-calculator.com) to help guide decisions about extended ET**
- **All patients with ≥4 nodes should receive extended ET (no evidence to use BCI or other tools). ASCO, Andre F et al. JCO 2022**

Zhang Y, et al. Clin Cancer Res. 2013;19(15):4196-4205. 2. Sgroi DC, et al. J Natl Cancer Inst. 2013;105(14):1036-1042. 3. Bartlett JMS, et al. Ann Oncol. 2019;300(11):1776-1783. 4. Noordhoek I, et al. Clin Cancer Res. 2021;27(1):311-319. 5. Mamounas EP, et al. Abstract 501: ASCO June 2021. 6. Simon RM, et al. J Natl Cancer Inst. 2009;101(21):1446-1452.

Pratt discussion, ESMO 2022

NCCN Guidelines: Gene Expression Assays for Consideration of Adjuvant Systemic Therapy

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene (Oncotype Dx) (for pN0)	Yes	Yes	Preferred	1
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)	Yes	Yes	Postmenopausal: Preferred	1
			Premenopausal: Other	2A
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A

National Comprehensive Cancer Network (NCCN®). NCCN clinical practice guidelines in oncology. Breast cancer — Version 5.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 2024.

Adjuvant Abemaciclib in HR+/HER2−, Node-Positive, High-Risk EBC

Phase 3 monarchE Study Design

Key eligibility criteria:

- HR-positive/HER2-negative high-risk EBC
- Women or men
- Premenopausal/ postmenopausal
- With or without prior neoadjuvant *and/or* adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 mo from surgery to randomization and 12 wks of ET after last non-ET

ITT includes both Cohort 1 and Cohort 2

91%

Cohort 1: High-risk based on clinical pathological features

- ≥ 4 ALN *or*
- 1-3 ALN *and* ≥ 1 of the below:
  - Grade 3 disease
  - Tumor size ≥ 5 cm

9%

Cohort 2: High-risk based on Ki-67

- 1-3 ALN *and*
- Ki-67 ≥ 20% *and*
- No grade ≥ 3 tumor and tumor size not ≥ 5 cm

N = 5637

R 1:1

On-study treatment period (2 y)

Abemaciclib (150 mg twice daily) + **endocrine therapy**

Endocrine therapy

Stratified for

- Prior chemotherapy
- Menopausal status
- Region

Follow-up period

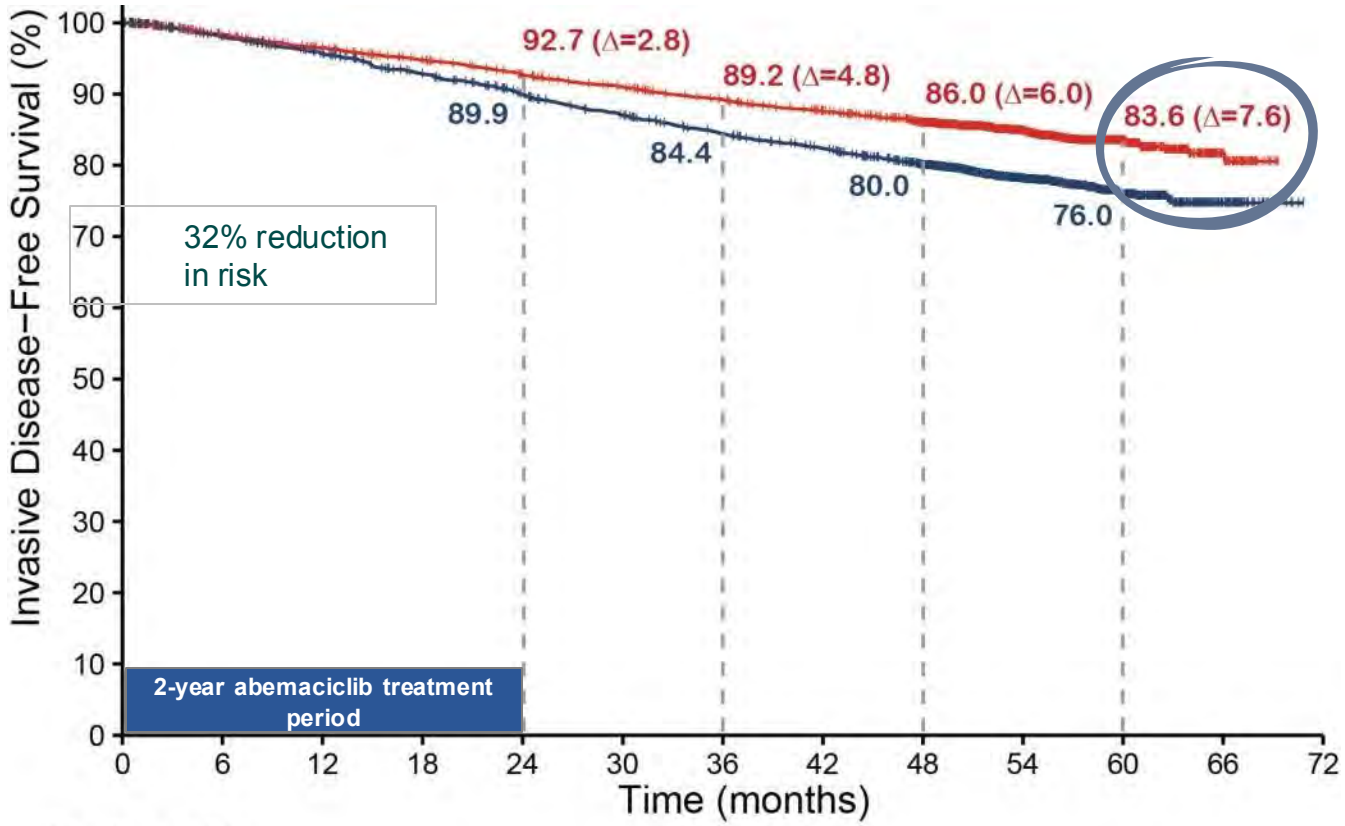
Endocrine therapy 3 to 8 y, as clinically indicated

Primary objective: IDFS

Secondary objectives: IDFS (high Ki-67), DRFS, OS, safety, PK, PROs

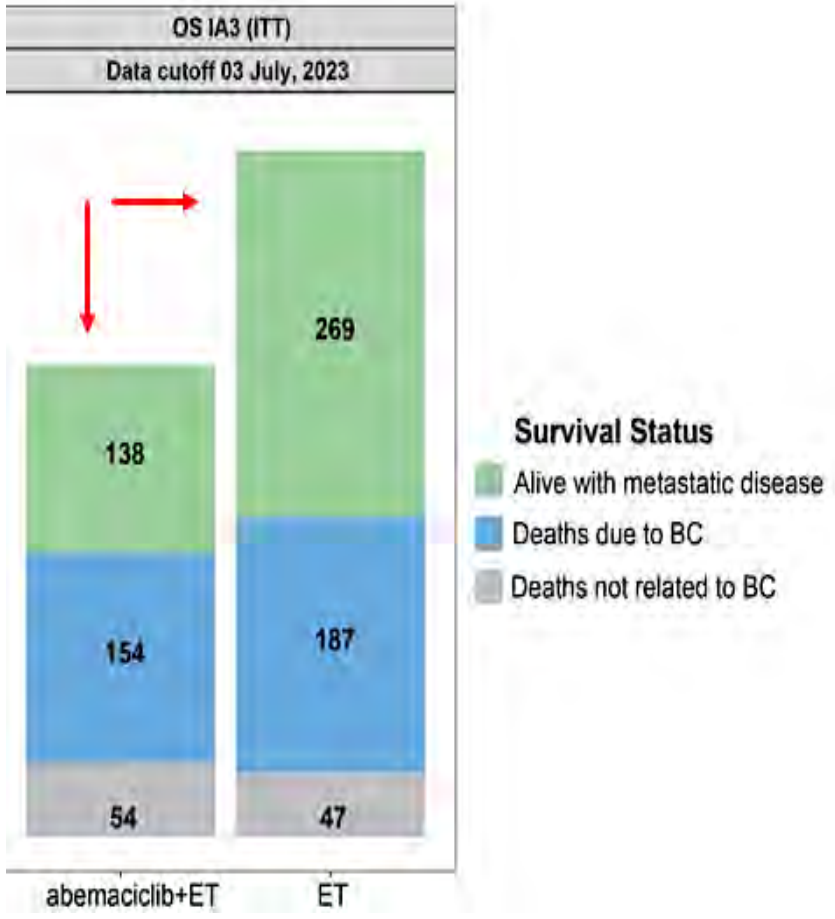
Harbeck ESMO 2023 Abstract LBA17

monarchE: 5-Yr Update Adjuvant Abemaciclib in HR+/HER2- EBC
IDFS and OS in ITT



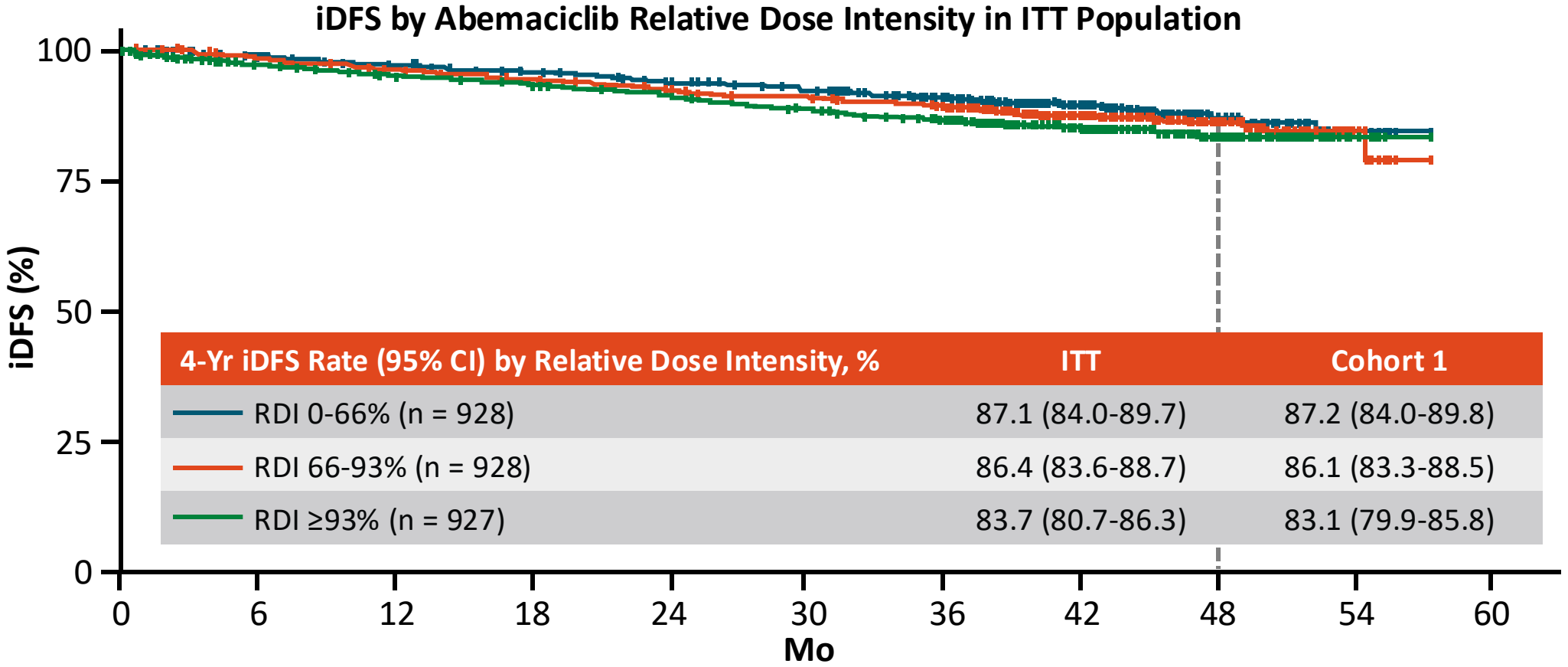
Number at risk

Abemaciclib + ET	2808	2621	2549	2479	2408	2347	2284	2220	2095	1175	490	74	0
ET alone	2829	2653	2573	2474	2374	2281	2195	2125	1974	1124	473	67	0



Rastogi P et al. *J Clin Oncol* 2024 Mar 20;42(9):987-93;
Harbeck ESMO 2023 Abstract LBA17

monarchE: Dose Reductions and Efficacy of Adjuvant Abemaciclib



4-Yr iDFS Rate (95% CI) by Relative Dose Intensity, %	ITT	Cohort 1
RDI 0-66% (n = 928)	87.1 (84.0-89.7)	87.2 (84.0-89.8)
RDI 66-93% (n = 928)	86.4 (83.6-88.7)	86.1 (83.3-88.5)
RDI ≥93% (n = 927)	83.7 (80.7-86.3)	83.1 (79.9-85.8)

- Dose reductions were not associated with decreased benefit
- Similar efficacy for maintaining full dose vs reducing dose when accounting for timing of dose reductions

O'Shaughnessy et al. ESMO 2023. Abstr 274P.

FDA Approves Ribociclib with an Aromatase Inhibitor and Ribociclib in Combination with Letrozole for Localized High-Risk Breast Cancer

Press Release: September 14, 2024

"The Food and Drug Administration approved ribociclib with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence. Additionally, FDA also approved the ribociclib and letrozole co-pack for the same indication.

Efficacy of ribociclib with a non-steroidal aromatase inhibitor (NSAI) was evaluated in NATALEE (NCT03701334), a randomized, open-label, multicenter trial in 5101 adults with HR-positive, HER2-negative early breast cancer. The trial included patients with any lymph node involvement (excluding microscopic nodal involvement), or if there was no nodal involvement, either tumor size > 5 cm, or tumor size 2 to 5 cm with either Grade 2 (and high genomic risk or Ki67 ≥ 20%) or Grade 3. The main efficacy outcome measure was invasive disease-free survival (iDFS). A statistically significant improvement in iDFS was observed in the intent-to-treat patient population at an interim analysis. Efficacy results at the final iDFS analysis showed that iDFS at 36 months was 90.7% in the ribociclib + NSAI arm and 87.6% in the NSAI arm, with a hazard ratio of 0.749. At the time of the iDFS final analysis, OS was immature.

In the adjuvant treatment setting, the recommended ribociclib dose is 400 mg (two 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles. Refer to the prescribing information for the recommended dosage of the aromatase inhibitor. Ribociclib has newly updated storage conditions. Ribociclib should now be refrigerated until dispensed to patients. After dispensing, healthcare providers should advise patients to store ribociclib at room temperature for up to 2 months."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ribociclib-aromatase-inhibitor-and-ribociclib-and-letrozole-co-pack-early-high-risk-0

NATALEE: Study Design and Methods

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **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]

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

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

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

Primary End Point
- iDFS using STEEP criteria

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

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

Endpoints included in this presentation

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan-Meier method

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

Data cutoff: 29 April 2024

ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.

[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.

1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS597. **3.** Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. **4.** Hortobagyi, G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

NATALEE: Patient Disposition

All patients are off RIB, and 62.8% completed the 3-year duration

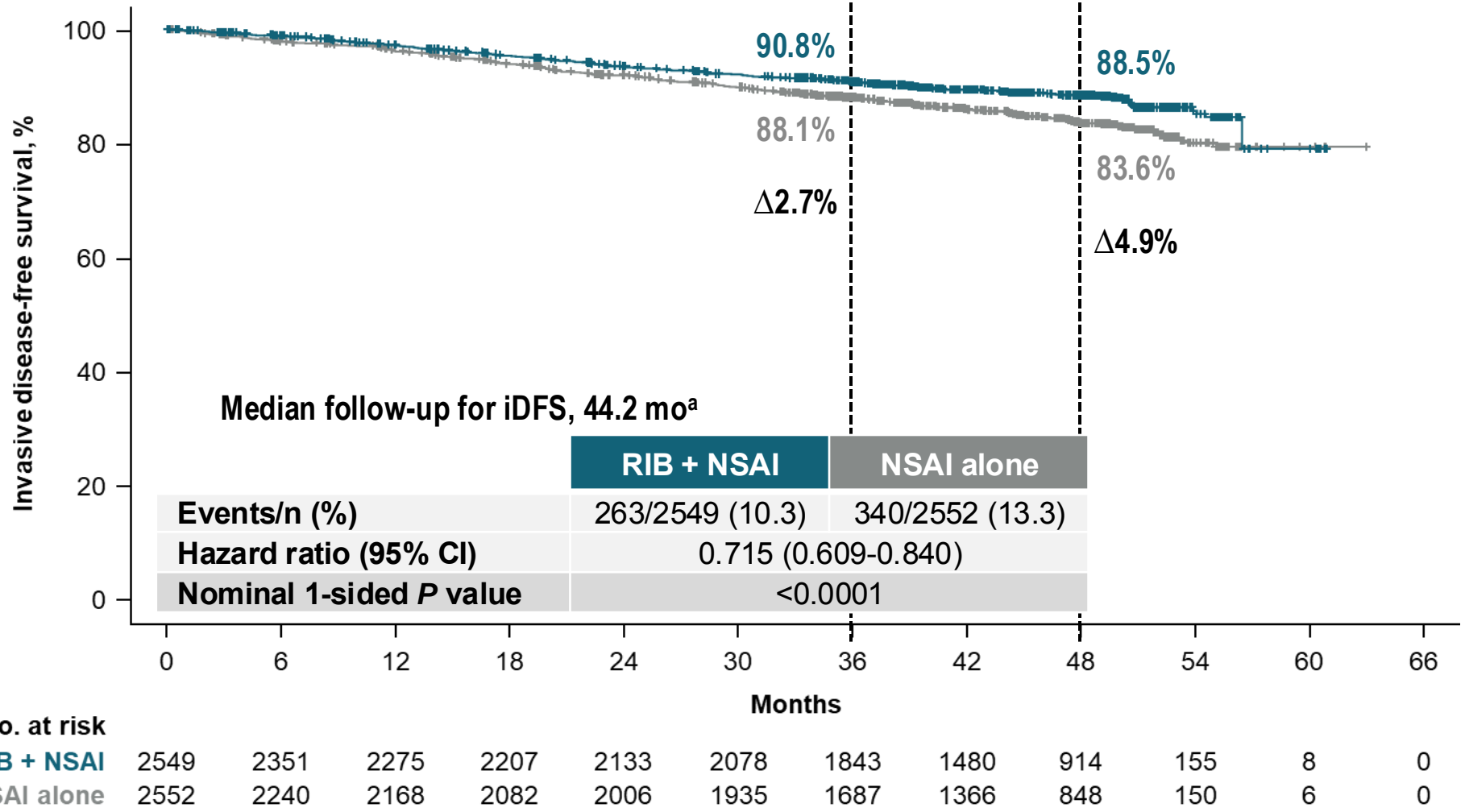
n (%)	RIB + NSAI n=2549		NSAI alone n=2552
Randomized	2549 (100)		2552 (100)
Treated	2526 (99.1)		2441 (95.7)
NSAI treatment ongoing	1794 (70.4)		1628 (63.8)
Completed 3 y RIB treatment	1601 (62.8)		–
Completed 5y study treatment	10 (0.4)		9 (0.4)
	RIB	NSAI	NSAI
Early discontinuation	923 (36.2)	722 (28.3)	804 (31.5)
Primary reason for early discontinuation			
AE	509 (20.0)	136 (5.3)	124 (4.9)
Disease relapse	127 (5.0)	196 (7.7)	267 (10.5)
Patient/physician decision	160 (6.3)	206 (8.1)	189 (7.4)
Lost to follow-up	8 (0.3)	15 (0.6)	21 (0.8)
Death	5 (0.2)	9 (0.4)	6 (0.2)
Other[a]	114 (4.5)	160 (6.2)	197 (7.7)

- At the data cutoff, median duration of exposure to study treatment was 45.1 months in the RIB + NSAI arm vs 45.0 months in the NSAI alone arm

AE, adverse event; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Other includes withdrawal by patient, protocol deviation, among other reasons.

NATALEE: iDFS in ITT Population

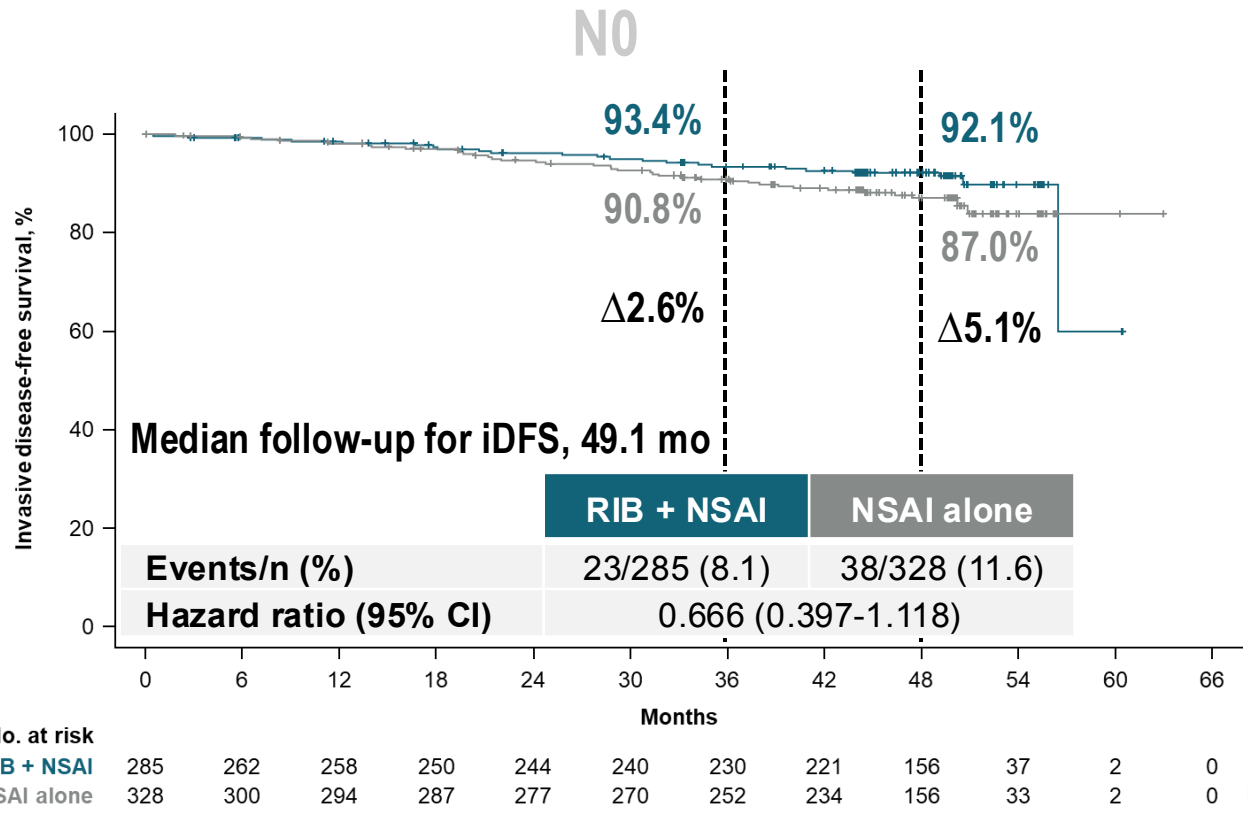
Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment

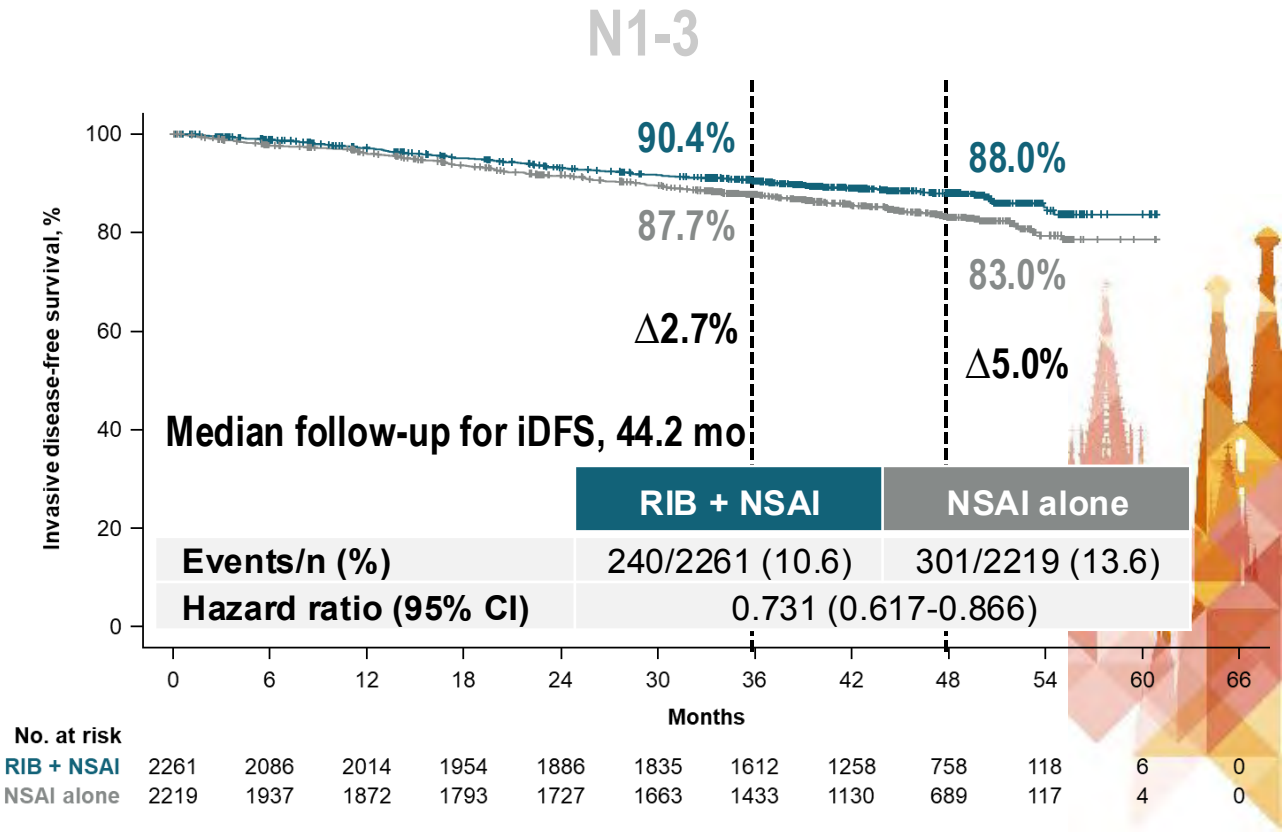


iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

NATALEE: iDFS by Nodal Status

RIB + NSAI showed an increasing magnitude of iDFS benefit over time for patients with N0 or N1-3 disease



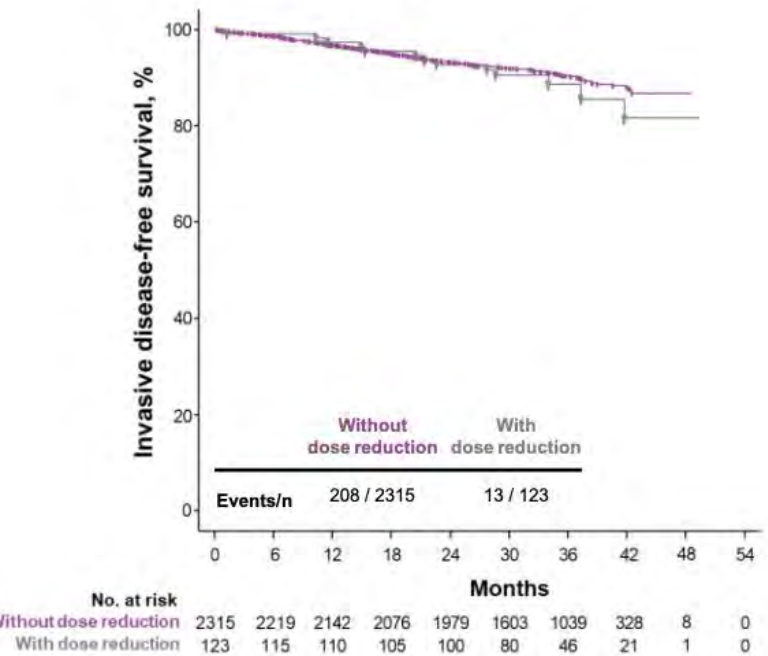


iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

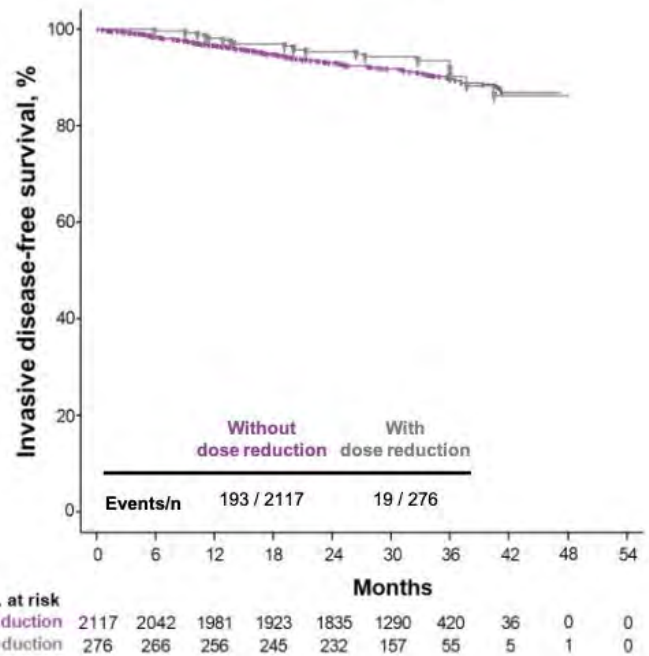
NATALEE: IDFS BY DOSE REDUCTIONS

Landmark analysis revealed that RIB dose reduction due to AEs did not impact efficacy

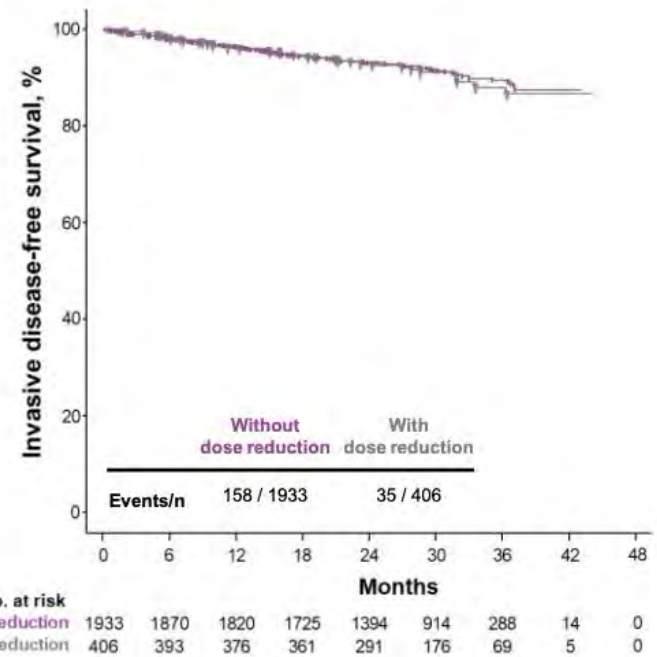
iDFS by Dose Reduction at 25th Percentile[a] (1.87 mo.)



iDFS by Dose Reduction at 50th Percentile[a] (3.17 mo.)



iDFS by Dose Reduction at 75th Percentile[a] (7.28 mo)

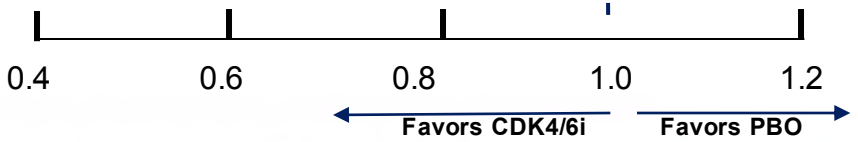


[a] Of dose reduction time, calculated from randomization

AE, adverse event; iDFS, invasive disease–free survival; RIB, ribociclib.

Overall Survival in MBC Patients Treated with CDK4/6i

		Treatment Arm: OS, Median, Mo	Placebo Arm: OS, Median, Mo	Hazard Ratio	Hazard Ratio (95% CI)	*P* Value	Significance reached vs placebo[a]
PAL	PALOMA-2[1] Palbociclib + letrozole	53.9	51.2		0.956 (0.777-1.177)	0.3378	✗
PAL	PALOMA-3[2] Palbociclib + fulvestrant	34.9	28.0		0.81 (0.64-1.03)	.09	✗
ABE	MONARCH 2[3] Abemaciclib + fulvestrant	46.7	37.3		0.76 (0.61-0.95)	.01	✓
ABE	MONARCH 3 Abemaciclib + NSAI	66.8	53.7		0.804 (0.637-1.015)	.0664	✗
RIBO	MONALEESA-2[4,5] Ribociclib + letrozole	63.9	51.4		0.76 (0.63-0.93)	.004	✓
RIBO	MONALEESA-7[6] Ribociclib + goserelin + tamoxifen/NSAI	NR	40.9		0.71 (0.54-0.95)	.00973	✓
RIBO	MONALEESA-3[7] Ribociclib + fulvestrant	NR	40.0		0.72 (0.57-0.92)	.00455	✓



[a] The red × denotes trials that did not report significant median OS compared with placebo. ABC, advanced breast cancer; ABE, abemaciclib; NR, not reached; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; RIBO, ribociclib; PAL, palbociclib. 1. Finn RS, et al. J Clin Oncol. 2022; 40 (suppl 17; abstr LBA1003). 2. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. 3. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 4. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 5. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR. 6. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 7. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524.

postMONARCH as 2L ER+ MBC

Investigator-Assessed PFS

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

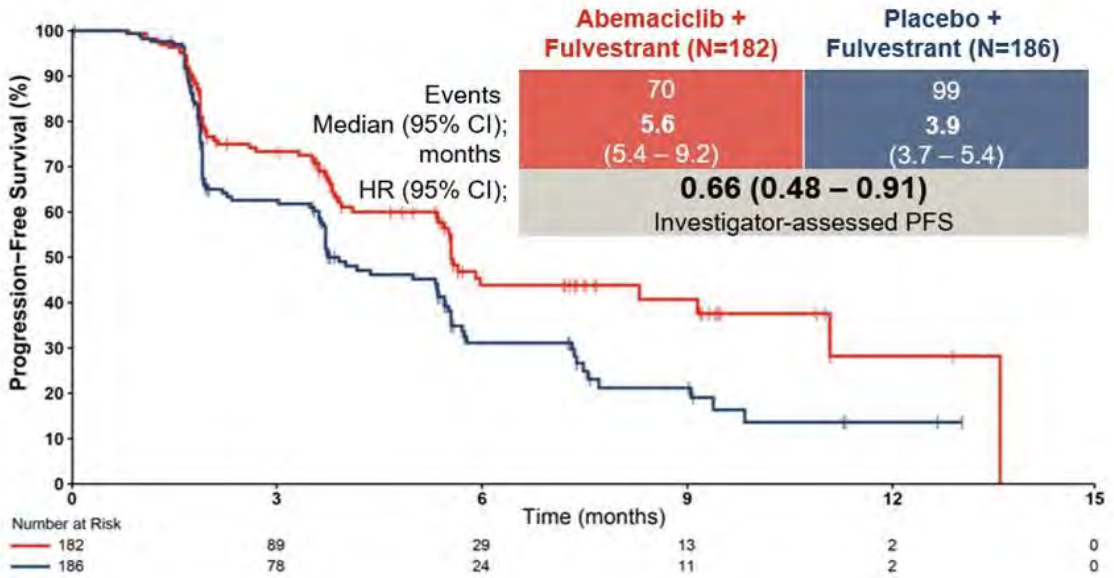
Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

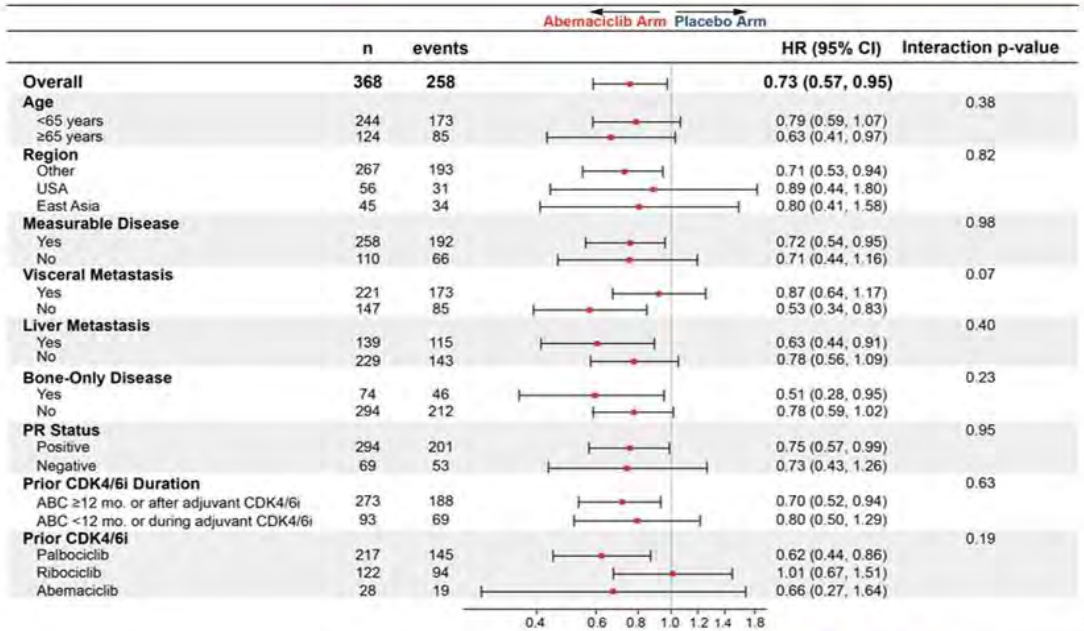
Randomization 1:1

N = 368

- Abemaciclib + Fulvestrant
- Placebo + Fulvestrant

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestrant N=186 (%)
Measurable Disease		72	68
Visceral metastasis		62	59
Site of Metastasis	Liver	37	38
	Bone-Only	18	23
Prior CDK4/6i Setting	ABC	100	98
	Adjuvant	0	2
Prior CDK4/6i	Palbociclib	59	59
	Ribociclib	34	33
	Abemaciclib	8	8
Prior CDK4/6i Duration	≥12 months*	71	77
	<12 months^	29	22

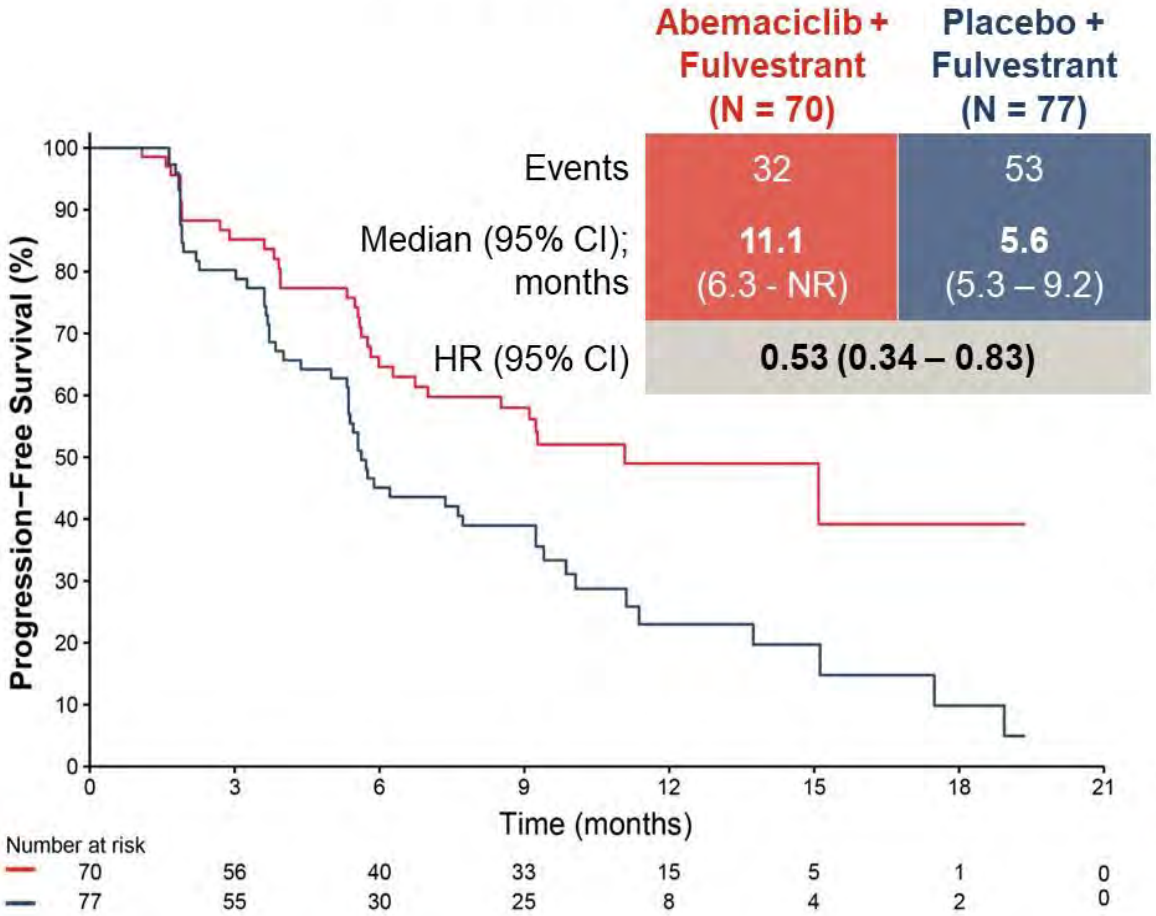




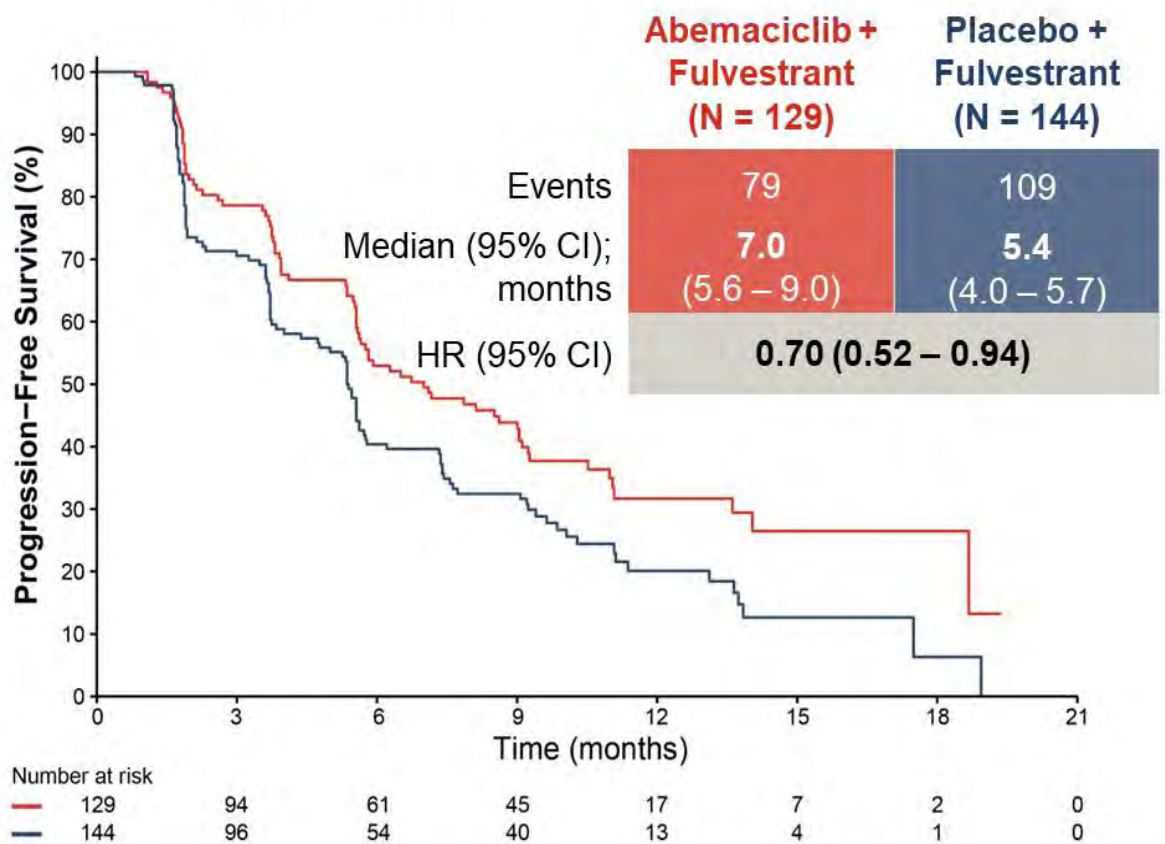
postMONARCH as 2L ER+ MBC

Investigator-Assessed PFS

No visceral metastasis



Prior CDK4/6i Duration ≥ 12 months*



* ≥ 12 months ABC or recurrence on EBC therapy

FDA Approves Inavolisib for Endocrine-Resistant, HR-Positive, HER2-Negative Metastatic Breast Cancer with a PIK3CA Mutation

Press Release: October 10, 2024

"The Food and Drug Administration approved inavolisib with palbociclib and fulvestrant for adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth-factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. FDA also approved the FoundationOne Liquid CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with inavolisib with palbociclib and fulvestrant.

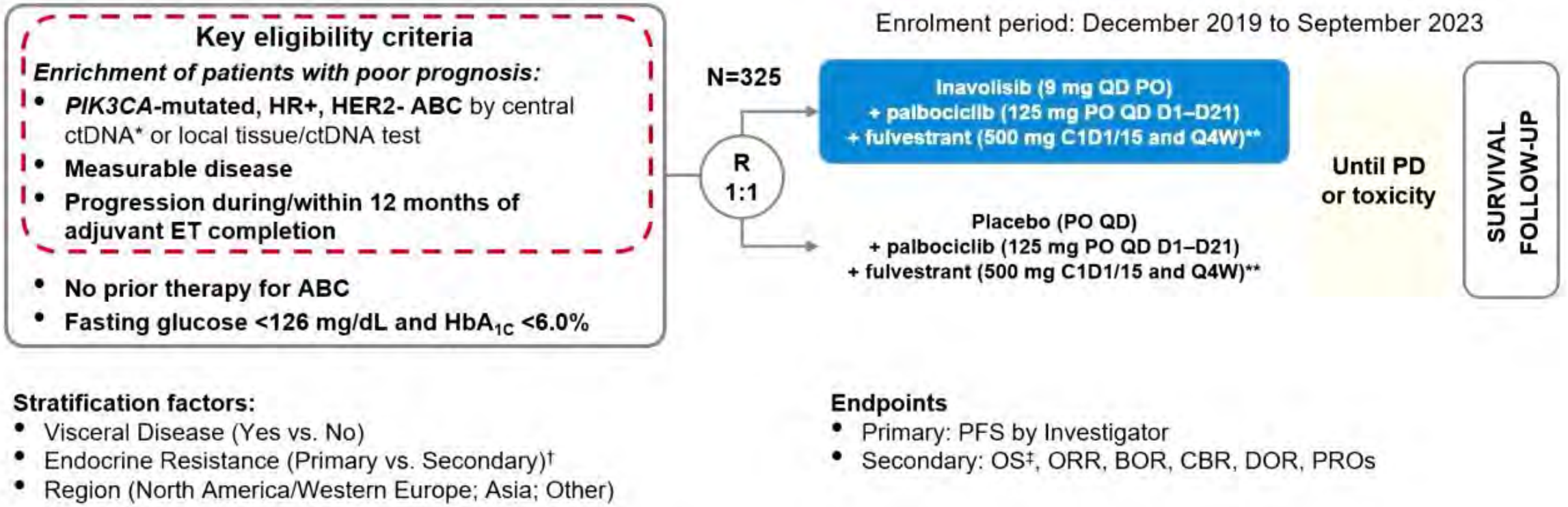
Efficacy was evaluated in INAVO120 (NCT04191499), a randomized, double-blind, placebo-controlled, multicenter trial in 325 patients with endocrine-resistant, PIK3CA-mutated HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic disease. Median PFS was 15.0 months in the inavolisib + palbociclib + fulvestrant arm and 7.3 months in the placebo + palbociclib + fulvestrant arm (Hazard ratio 0.43, *p*-value <0.0001). Interim analysis of overall survival based on 63% information fraction did not reach statistical significance but was supportive of the overall benefit risk assessment with a HR of 0.64.

The recommended inavolisib dose is 9 mg taken orally once daily, with or without food, until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive

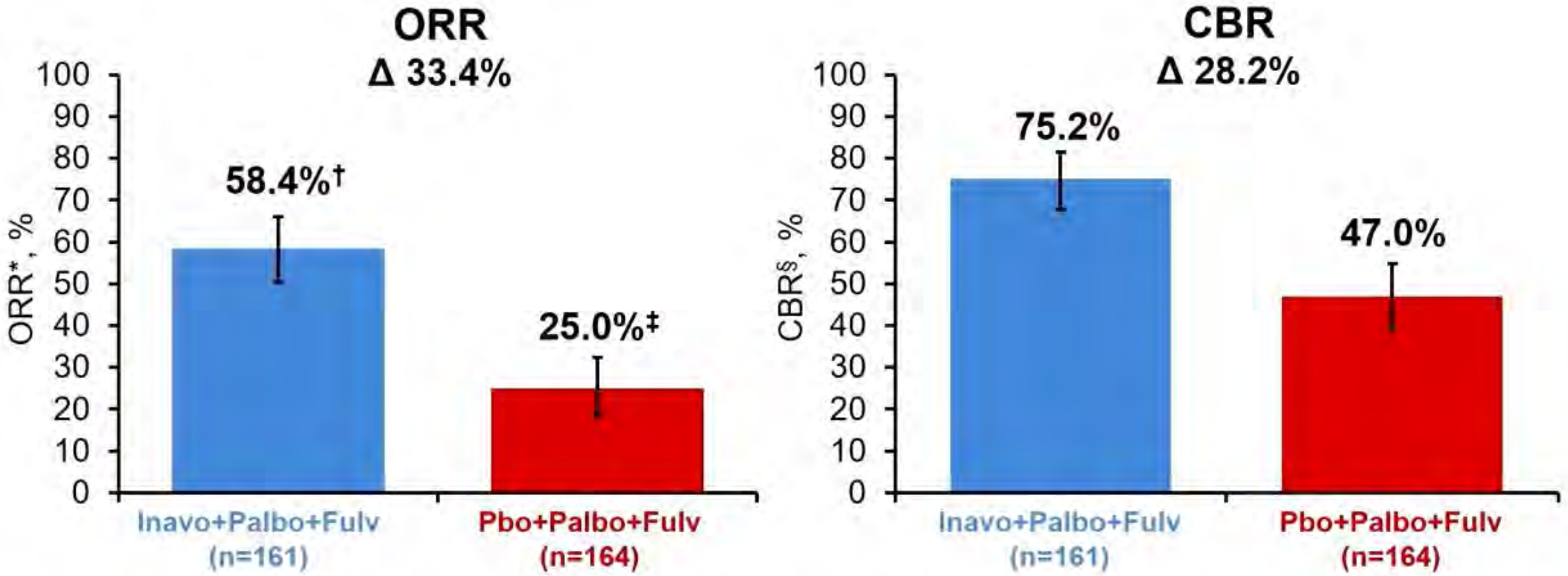
SABCS 2023: INAVO120 Primary Analysis

- More effective treatments for patients with PIK3CA mutations are needed
- Inavolisib is a highly potent and selective PIK3α inhibitor that also promotes degradation of mutant p110α, which may improve the therapeutic window



Komal Jhaveri, SABCS 2023

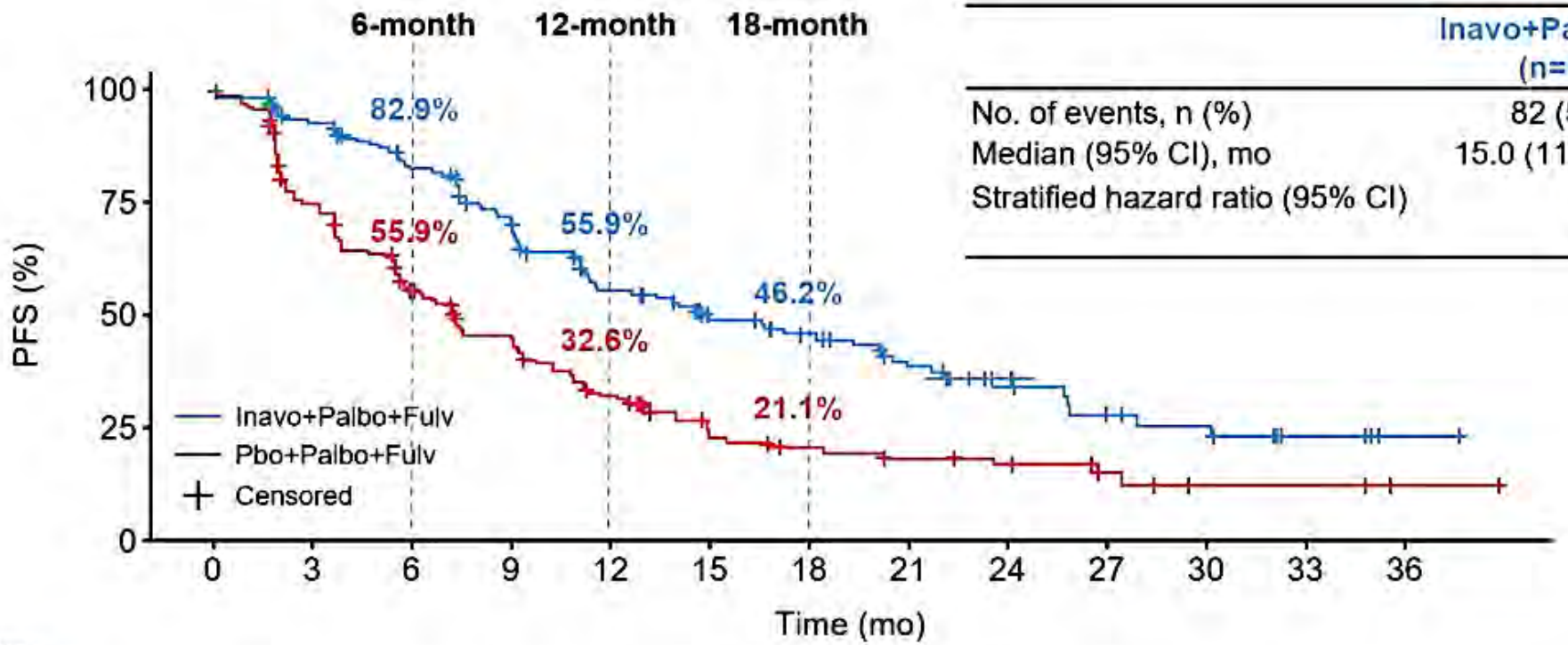
SABCS 2023: INAVO120 ORR and CBR



* Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Komal Jhaveri, SABCS 2023

SABCS 2023: INAVO120 PFS



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)**	
	p<0.0001	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

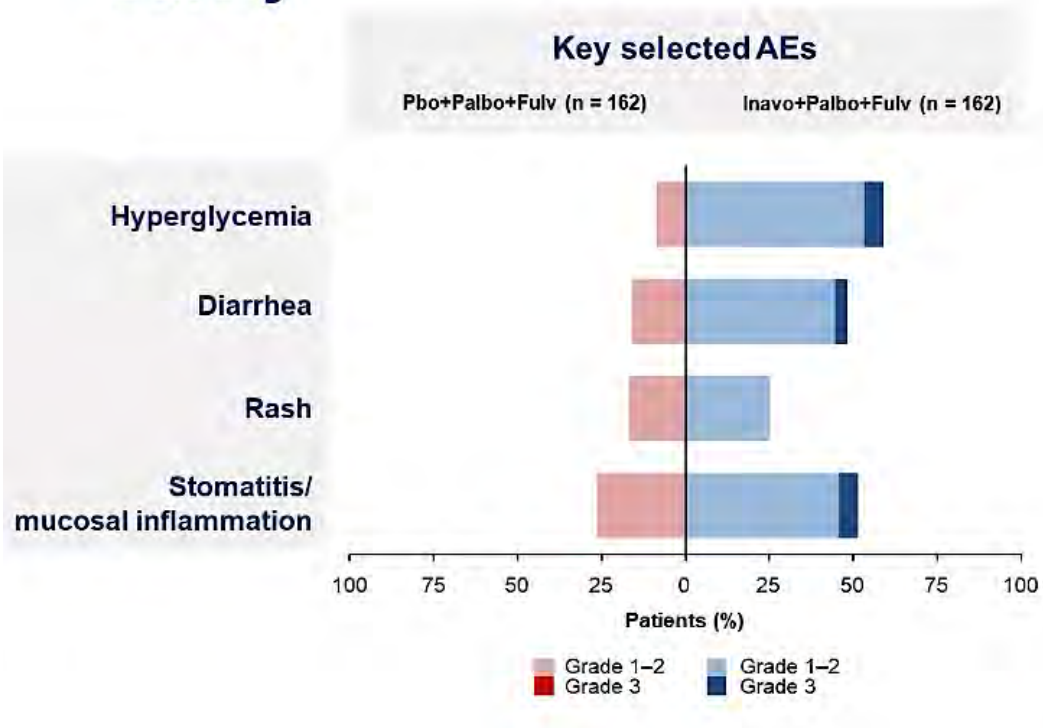
CCOD: 29th September 2023

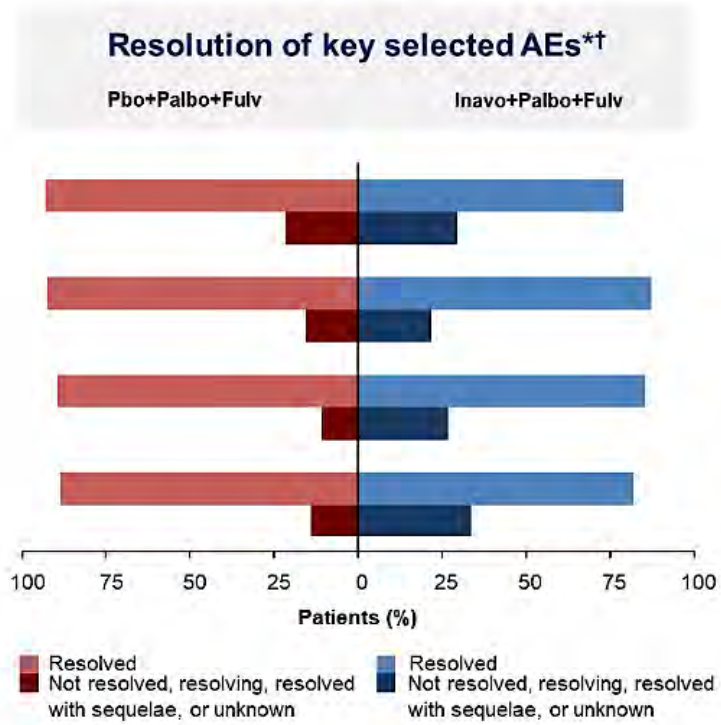
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Komal Jhaveri, SABCS 2023

INAVO120 Phase 3

Safety





Discontinuation rate of inavolisib due to any AE was 6.2%[1]

Patients, n (%)	Hyperglycemia	Diarrhea	Rash	Stomatitis/ mucosal inflammation
Inavolisib interruption due to AE	44 (27.2)	11 (6.8)	2 (1.2)	16 (9.9)
Inavolisib reduction due to AE	4 (2.5)	2 (1.2)	1 (0.6)	6 (3.7)
Inavolisib discontinuation due to AE	1 (0.6)*	0	0	1 (0.6)

Juric D, et al. ASCO 2024. Abstract 1003

Updates on Endocrine Therapy

- 3 yrs of ribociclib in high/intermediate risk pts improves iDFS and DRFS
- Adjuvant abemaciclib increasing improvement in IDFS at 5 years
- 2L MBC abemaciclib plus fulvestrant had superior PFS to fulvestrant alone – may be an option for 2L therapy after 1L CDK 4/6 inhibitor for patients who are not candidates for *mESR1, PIK3CA, AKT or PTEN*-directed therapy
- PI3K inhibitor inavolisib + fulvestrant + palbociclib in ET-resistant MBC approved by FDA for ET-resistant 1L pts with *PIK3CA*-mutant MBC and HgbA1c < 6%

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

Mass General Brigham
Mass General Cancer Center

Module 1: Management of Relapsed/Refractory HR-Positive Metastatic Breast Cancer

October 26th, 2024

Florida Cancer Specialists Retreat

Research To Practice

Orlando, FL

Seth A. Wander, MD, PhD

Assistant Professor of Medicine

Harvard Medical School

Massachusetts General Hospital

swander@mgh.harvard.edu

Management of Refractory HR+ MBC

- Evolving Therapeutic Landscape and Resistance Mechanisms

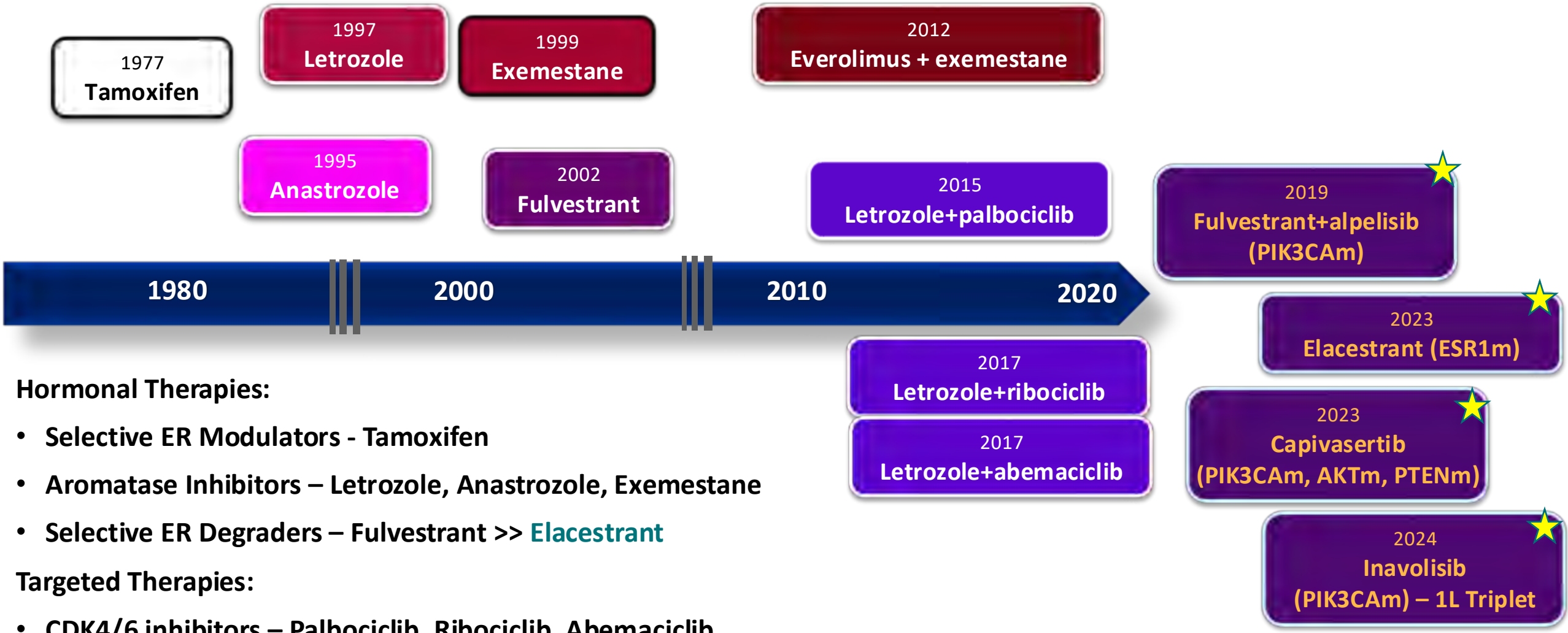
- EMERALD: Elacestrant (oral SERD) for Endocrine Refractory HR+ MBC
- Emerging Oral SERDS: Imlunestrant and Camizestrant

- CAPItello-291: Capivasertib (AKTi) for HR+ MBC with PI3K Pathway Alterations

- DESTINY-Breast06: Trastuzumab deruxtecan (ADC) for HER2-low MBC
- TROPiCS-02: Sacituzumab govitecan (ADC) for refractory HR+ MBC
- TROPION-Breast01: Datopotamab deruxtecan (novel ADC) for refractory HR+ MBC

- Shifting Therapeutic Approaches and Future Directions

Metastatic Breast Cancer: The Road to Personalized Therapy



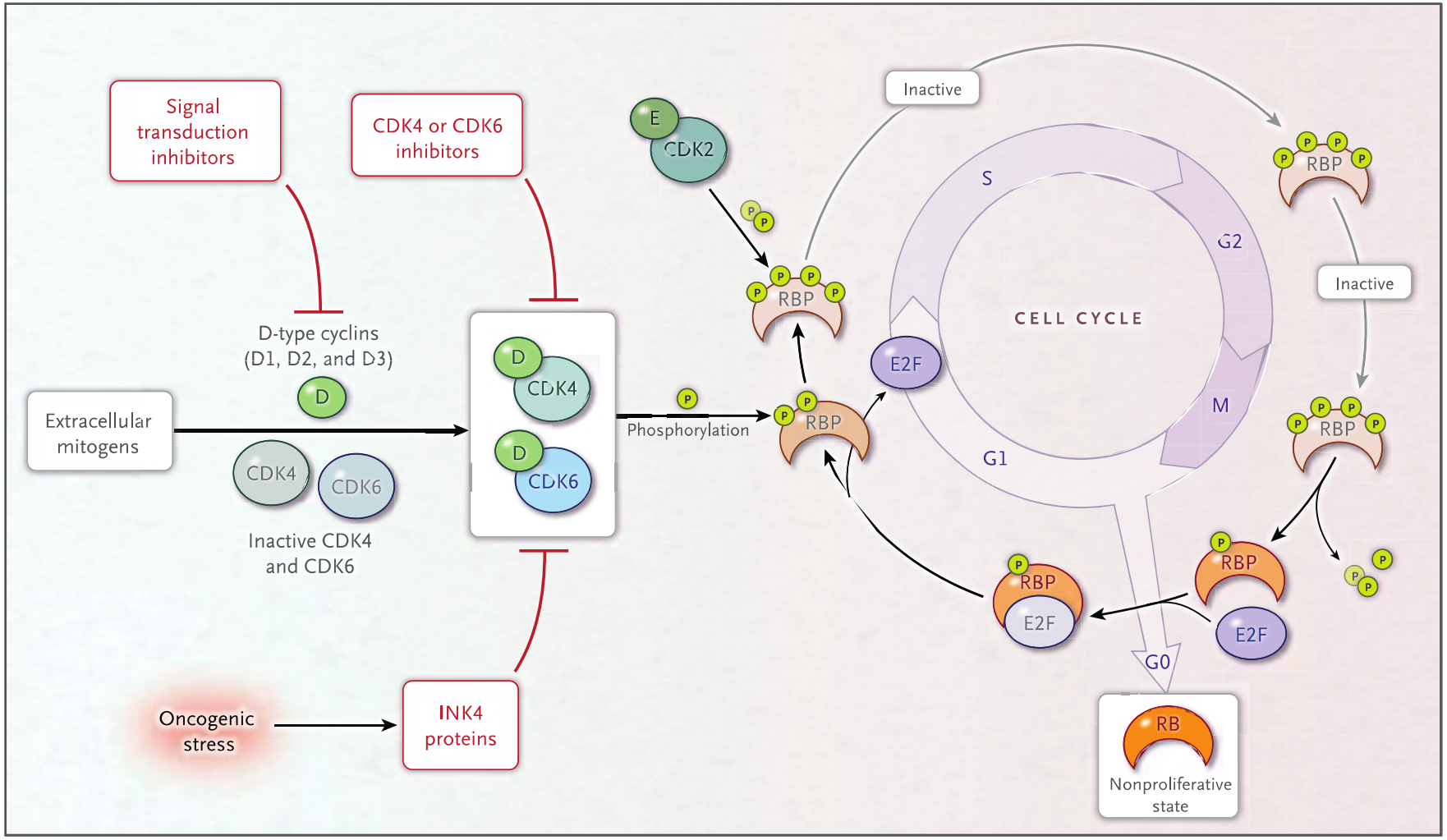
Hormonal Therapies:

- **Selective ER Modulators - Tamoxifen**
- **Aromatase Inhibitors – Letrozole, Anastrozole, Exemestane**
- **Selective ER Degraders – Fulvestrant >> Elacestrant**

Targeted Therapies:

- **CDK4/6 inhibitors – Palbociclib, Ribociclib, Abemaciclib**
- **PI3K, mTOR, AKT inhibitors – Everolimus, Alpelisib, Capivasertib, Inavolisib**

Signal Transduction via CDK-Rb-E2F



Sherr CJ et al NEJM 2016

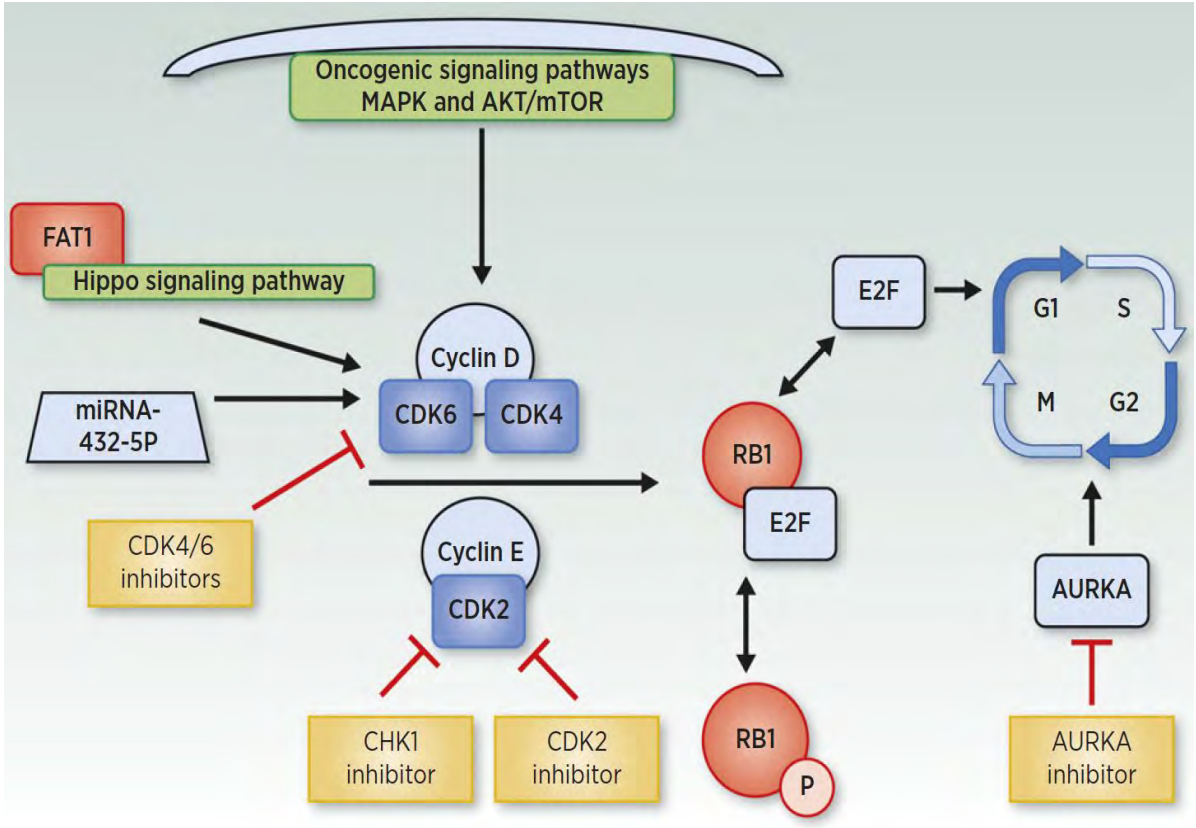
Resistance Drivers Define New Therapeutic Targets

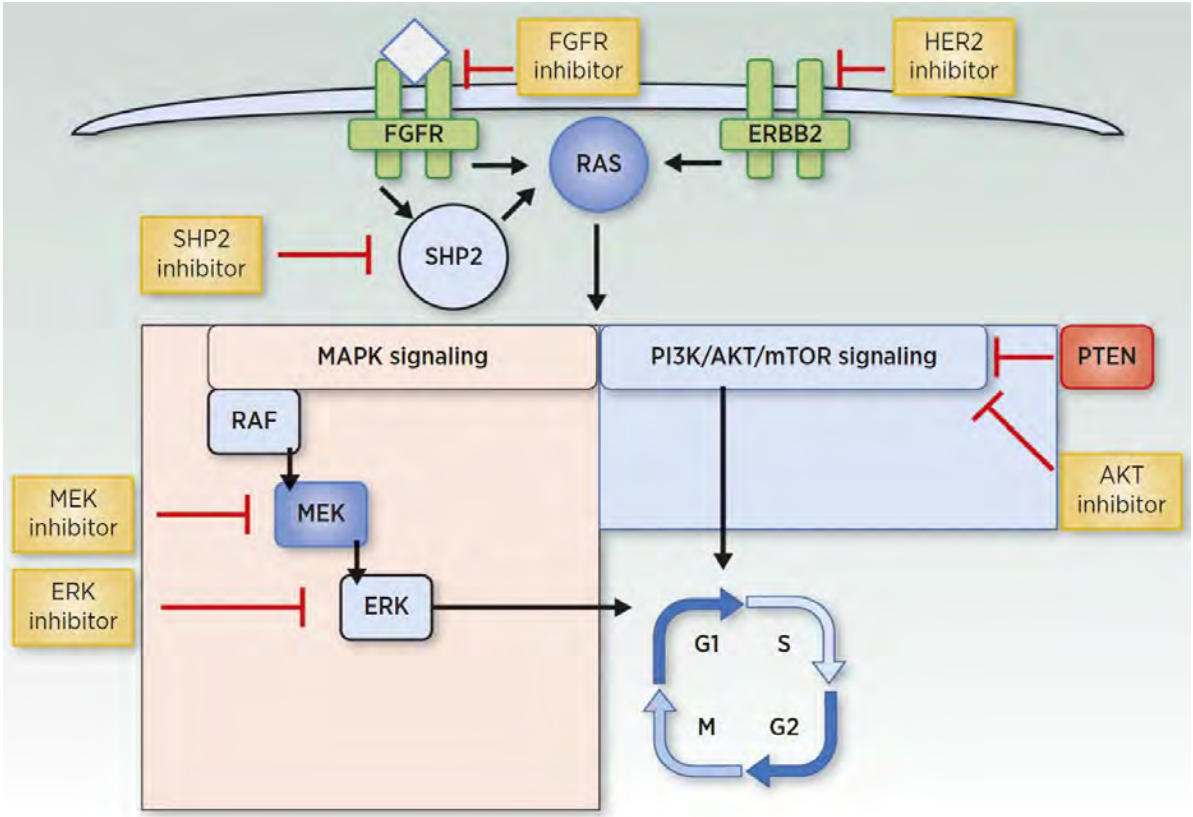
Cell cycle regulators

CCNE/CDK2
RB1/AURKA
FAT1/CDK6

Oncogenic growth signaling mediators

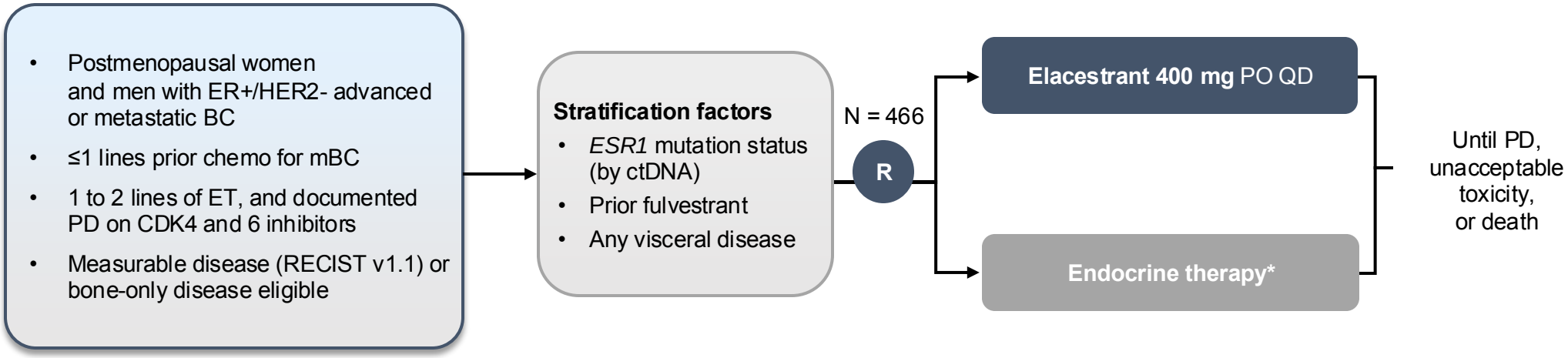
Receptor tyrosine kinases
RAS / MAPK pathway
PI3K/AKT/mTOR pathway





Lloyd MR et al CCR 2022

EMERALD: Elacestrant, Phase III



- **Primary endpoint:** PFS by BICR in all patients and in patients with mutant *ESR1*
  - Overall population (power ≥ 90% for HR of 0.667) or *ESR1*-mutated subset (power ≥ 80% for HR 0.610) at an overall α level of 5%
- **Secondary endpoints:** OS, PFS by BIRC in patients with WT *ESR1*, PFS by investigator review, ORR, DoR, CBR, safety, PK, and QOL

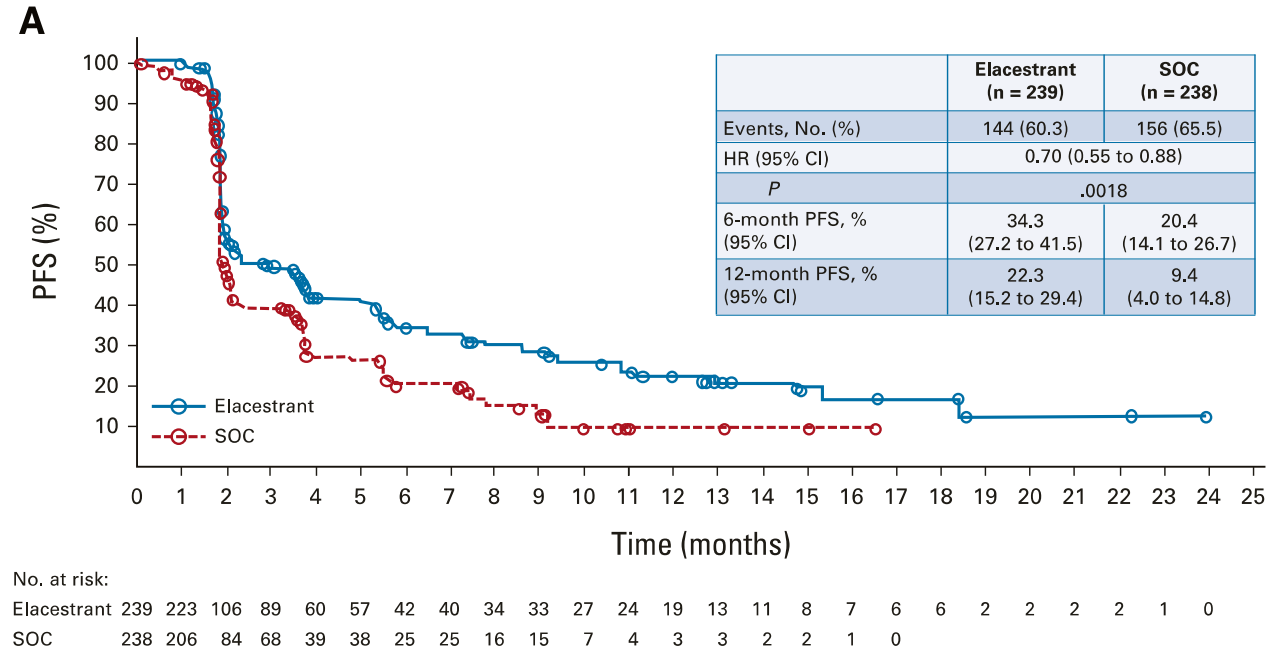
*Investigator's choice of fulvestrant 500 mg IM on days 1 and 15 of cycle 1 and then on day 1 of 28-day cycles or an AI (continuous dosing of anastrozole 1 mg/day, letrozole 2.5 mg/day, or exemestane 25 mg/day).
BIRC, blinded independent review committee; CBR, clinical benefit rate; IM, intramuscular; PD, progressive disease; PK, pharmacokinetics; QOL, quality of life.

Bardia A, et al. J Clin Oncol. 2020;38(suppl): Abstract TPS1104.

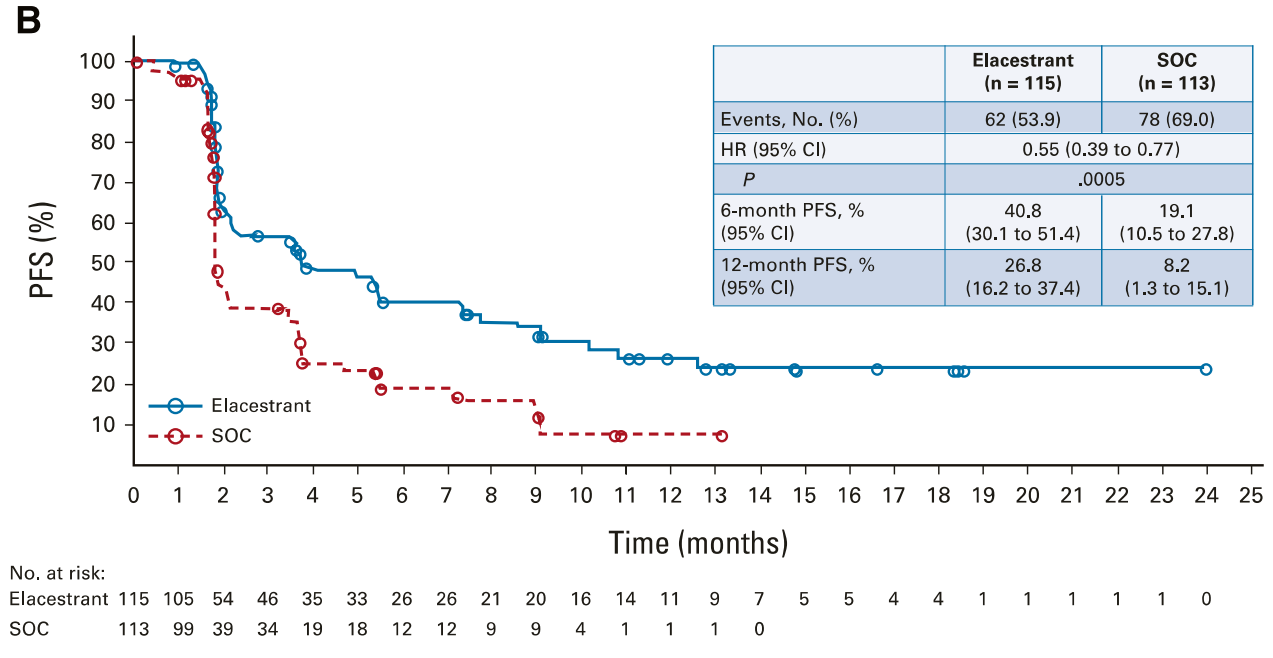
EMERALD: Elacestrant Efficacy

Patient Characteristics: Elacestrant vs. Control

- Prior Chemotherapy: 20% vs 24%
- ESR1m: 48% vs 47%
- Two prior lines of ET: 46% vs 41%



	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)



	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)

Median PFS Improvements:

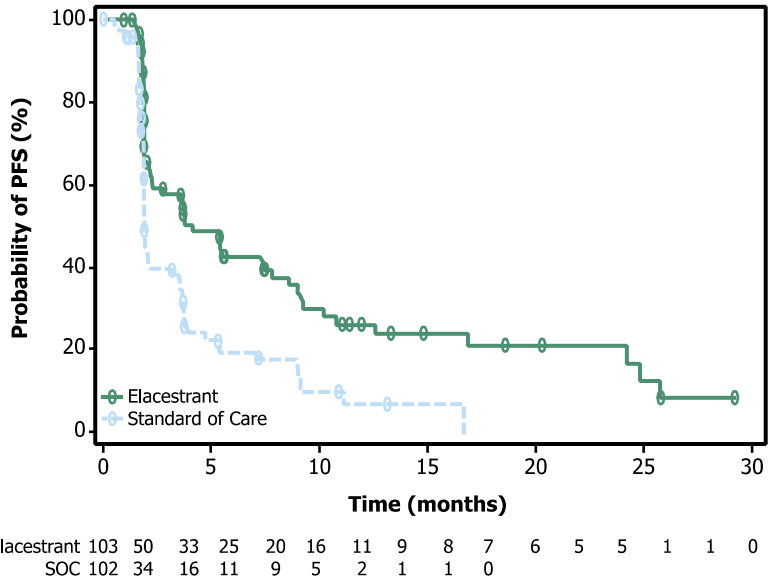
ITT: 1.94 > 2.79m; HR (95%CI) 0.68 (0.52-0.90), p=0.0049

ESR1m: 1.87 > 3.78m; HR (95%CI) 0.50 (0.34-0.74), p=0.0005

Bidard FC et al JCO 2022

EMERALD: Elacestrant Efficacy in ESR1m

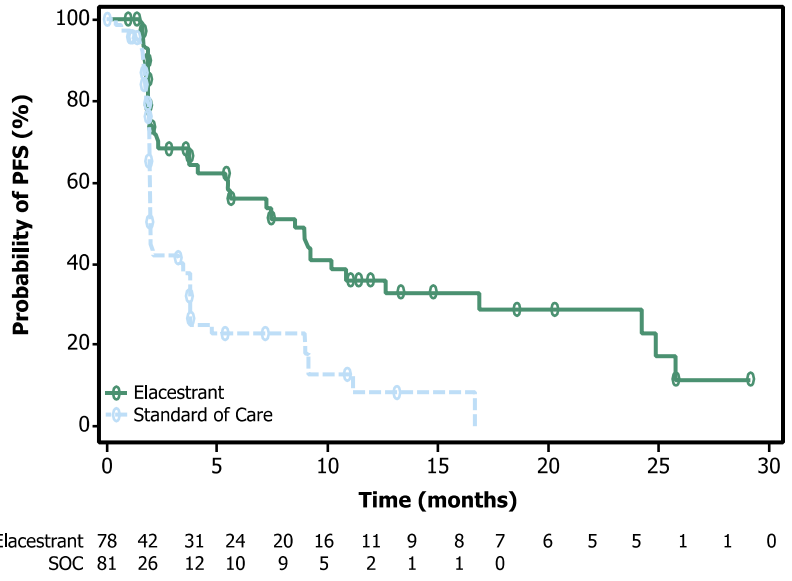
At least 6 mo CDK4/6i



Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0
SOC	102	34	16	11	9	5	2	1	1	0						

	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)	

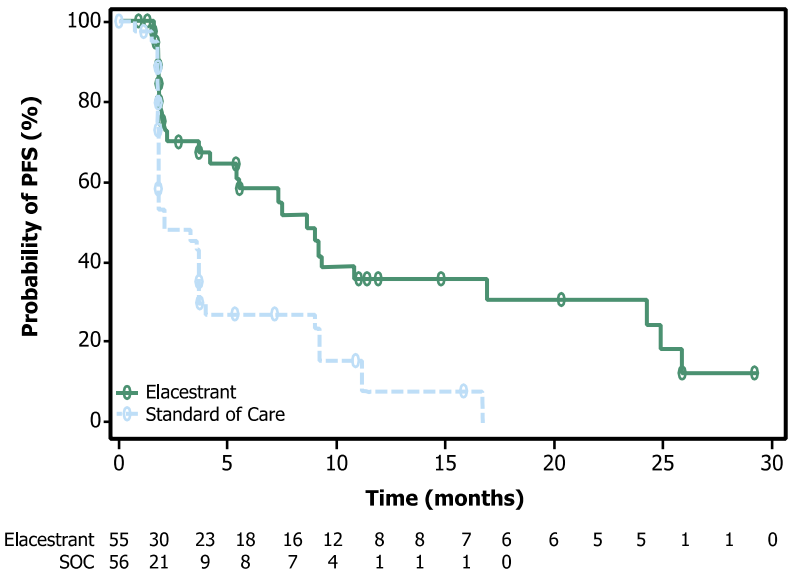
At least 12 mo CDK4/6i



Elacestrant	78	42	31	24	20	16	11	9	8	7	6	5	5	1	1	0
SOC	81	26	12	10	9	5	2	1	1	0						

	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)	

At least 18 mo CDK4/6i



Elacestrant	55	30	23	18	16	12	8	8	7	6	6	5	5	1	1	0
SOC	56	21	9	8	7	4	1	1	1	0						

	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)	

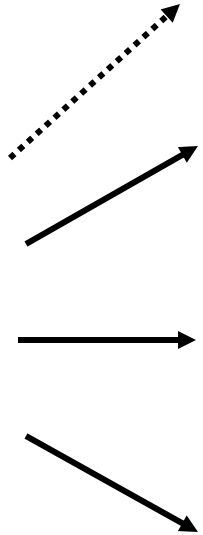
Bardia et al SABCS 2022 and CCR 2024

SERENA-2: Phase II, Camizestrant vs Fulvestrant

Postmenopausal women with ER+/HER2- advanced/metastatic breast cancer, n=240

- candidates for fulvestrant monotherapy;
- measurable and nonmeasurable disease;
- recurrence/progression on ≥1 line of ET; ≤1 line of chemotherapy;
- No prior fulvestrant or oral SERD in advanced setting

Prior CDK4/6i, lung/liver metastases



Camizestrant 300 mg PO QD (n = 20) (stopped early*)

Camizestrant 75 mg PO QD (n = 74)

Camizestrant 150 mg PO QD (n = 73)

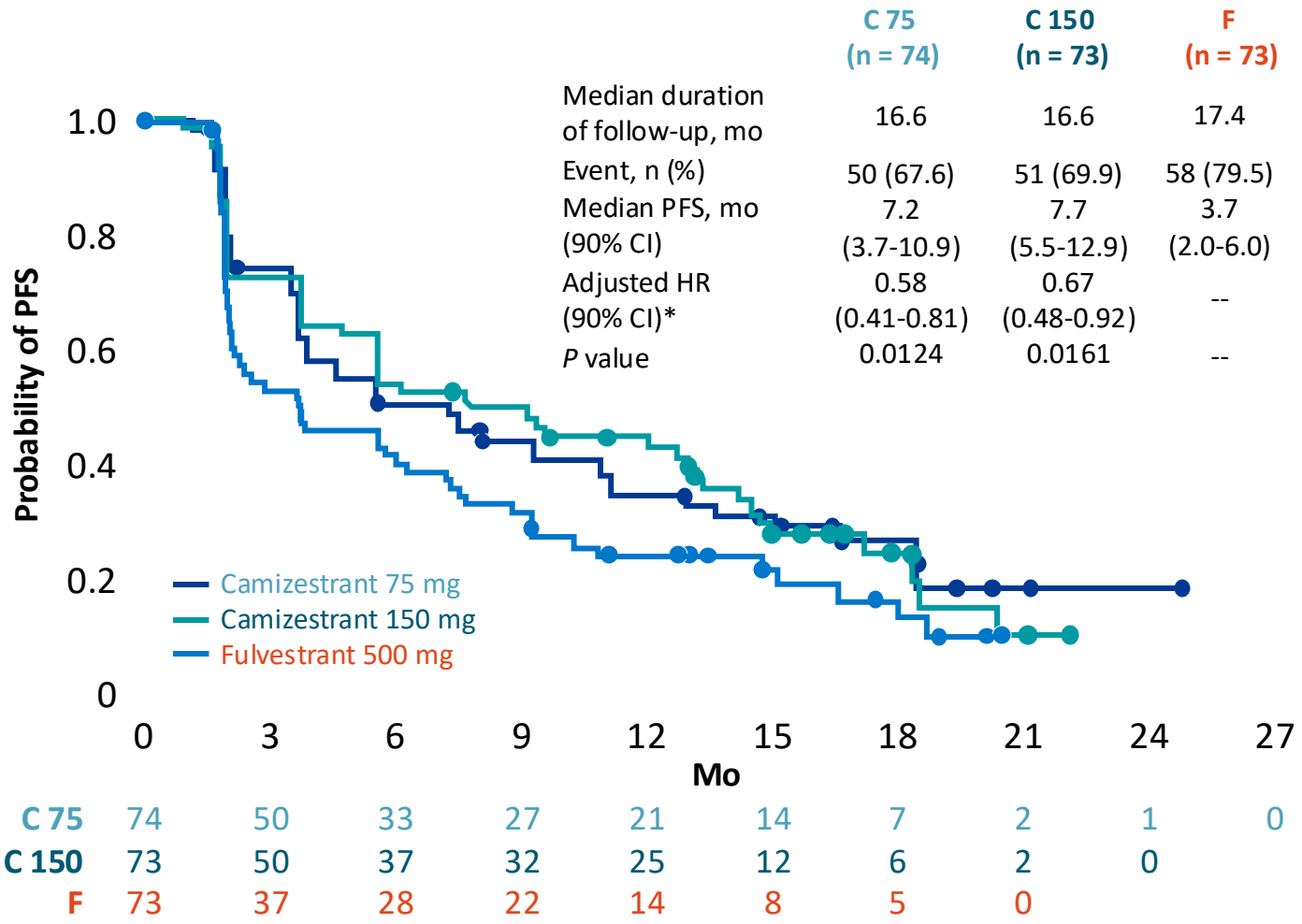
Fulvestrant 500 mg IM (n = 73)

*CSP v5 amendment: 16Dec20.

- **Primary Endpoint:** PFS
- **Secondary Endpoints:** CBR, ORR, OS, safety
- **Translational Endpoints:** ctDNA analysis, including *ESR1* mutations, CTC analysis

Oliveira et al SABCS 2022

SERENA-2: Camizestrant vs Fulvestrant PFS



	C 75 (n = 74)	C 150 (n = 73)	F (n = 73)
Median duration of follow-up, mo	16.6	16.6	17.4
Event, n (%)	50 (67.6)	51 (69.9)	58 (79.5)
Median PFS, mo (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)*	0.58 (0.41-0.81)	0.67 (0.48-0.92)	--
P value	0.0124	0.0161	--

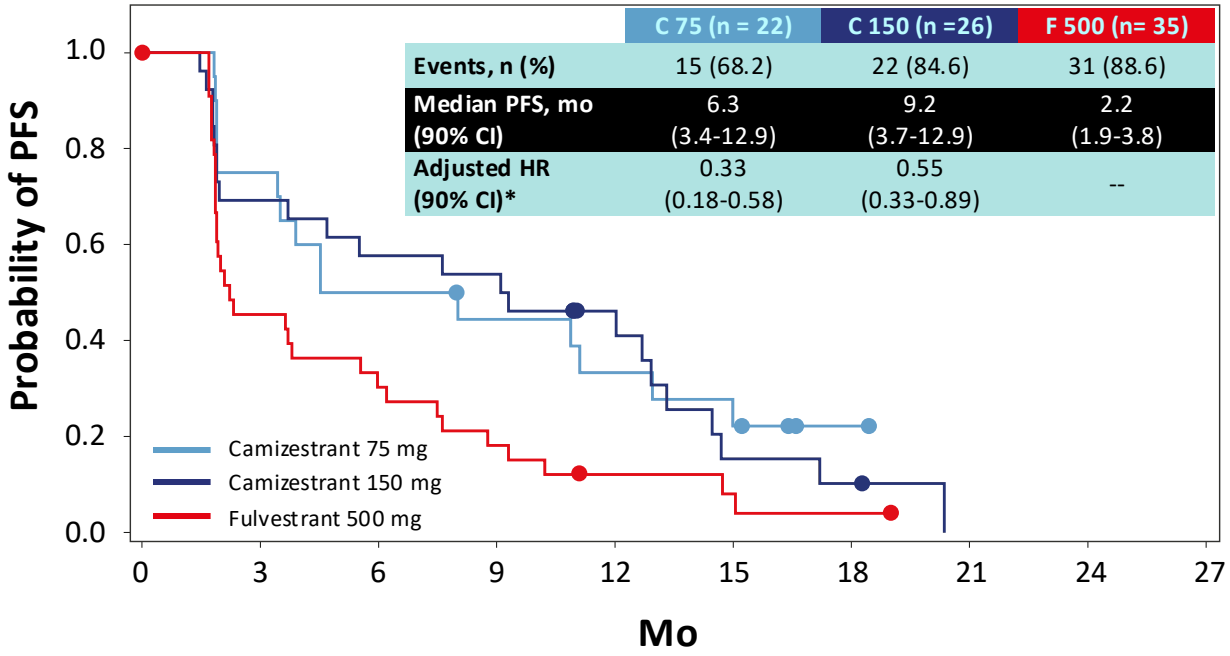
*HR adjusted for prior CDK4/6i and for lung/liver metastases.

Overall population:
Improvements in PFS with both 75mg and 150mg doses
~3.7m > 7-8m

Oliveira et al SABCS 2022

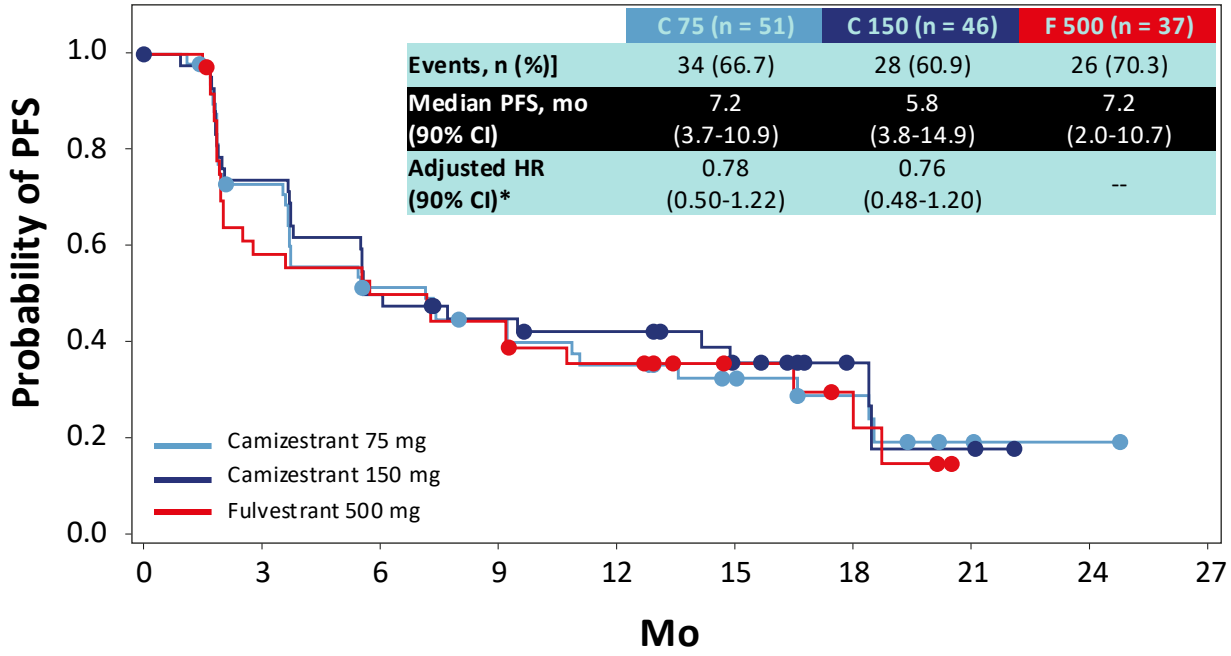
SERENA-2: PFS Outcomes by ESR1 Status

*ESR1*m Detectable at Baseline



C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m Not Detectable at Baseline



C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

Camizestrant provokes benefit in the ESR1m subpopulation compared to fulvestrant

Median PFS ~2.2m>6.3m>9.2m

*HRs adjusted for prior use of CDK4/6i and liver/lung metastases.

Oliveira et al SABCS 2022

Key Ongoing/Completed Metastatic Antiestrogen Trials

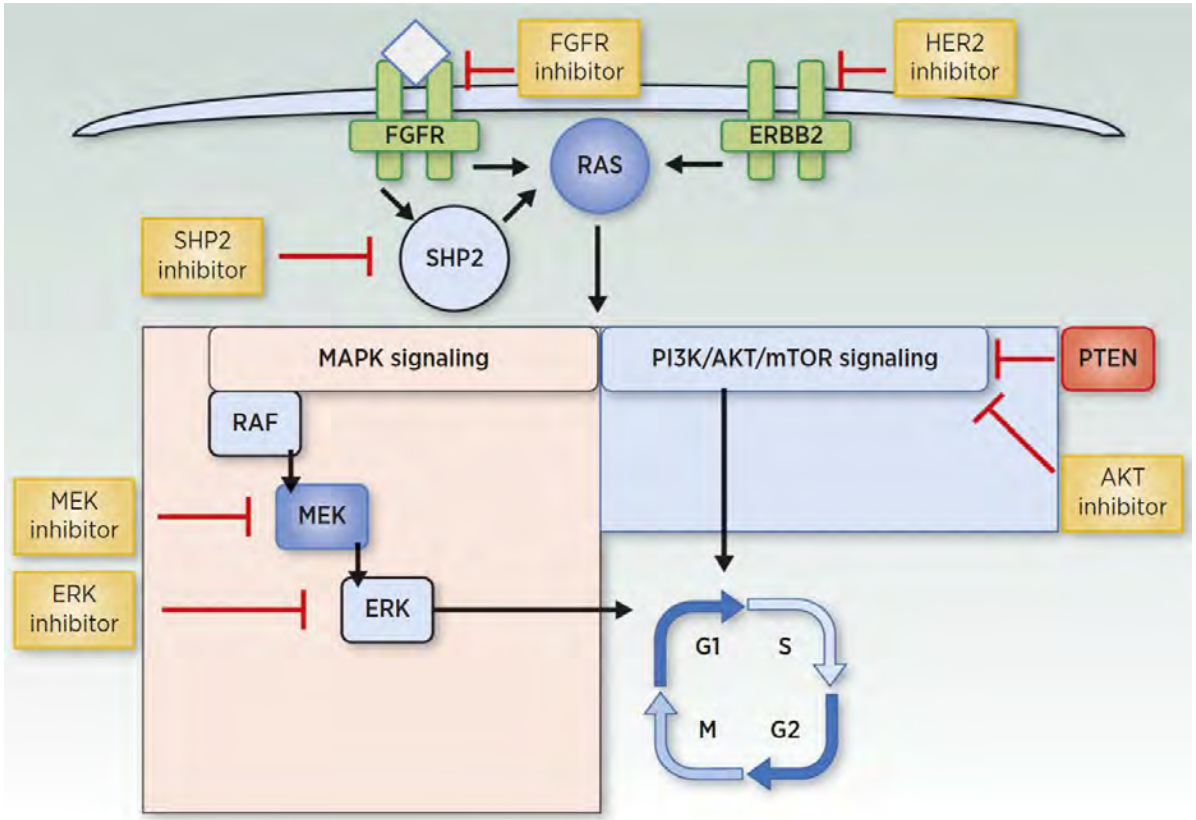
Agent	**Elacestrant**	**Camizestrant**	**Imlunestrant +/- Abema**	**Vepdegestrant**	**Lasofoxifene + Abema**	**Amcenestrant**	**Giredestrant**
Mechanism	**SERD**	**SERD**	**SERD**	**PROTAC**	**SERM**	**SERD**	**SERD**
Study	EMERALD[1]	SERENA-2[2,3]	EMBER-3[4]	VERITAC-2[5]	ELAINE-3[6]	AMEERA-3[7,8]	acelERA[9,10]
Control	Fulvestrant/AI	Fulvestrant	Fulvestrant/AI	Fulvestrant	Fulvestrant + Abema	Fulvestrant/AI/Tam	Fulvestrant/AI
Phase (N)	Phase III (477)	Phase II (240)	Phase III (860)	Phase III (560)	Phase III (400)	Phase II (290)	Phase II (303)
Prior CDK4/6i	Required	Permitted	Permitted	Required	Required	Permitted	Permitted
Prior Fulvestrant	Allowed	Excluded	Excluded	Excluded	Excluded	Allowed	Allowed
Results	Positive	Positive	Ongoing	Ongoing	Ongoing	Negative	Negative

1. Bidard et al JCO. 2022. 2. NCT04214288. 3. Oliveira et al SABCS 2022. 4. NCT04975308. 5. NCT05654623 6. NCT05696626 7. NCT04059484
8. Tolaney et al JCO. 2023 9. NCT04576455. 10. Jimenez et al. ESMO 2022.

Resistance Drivers Define New Therapeutic Targets

Oncogenic growth signaling mediators

Receptor tyrosine kinases
RAS / MAPK pathway
PI3K/AKT/mTOR pathway



RTKs @ cell surface + external ligands

PI3K >>>>>> Activated PI3K

PTEN

Alpelisib

AKT

Capivasertib

Cellular Growth
Survival + Division
Motility + Metastasis

Lloyd MR et al CCR 2022

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- 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 CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

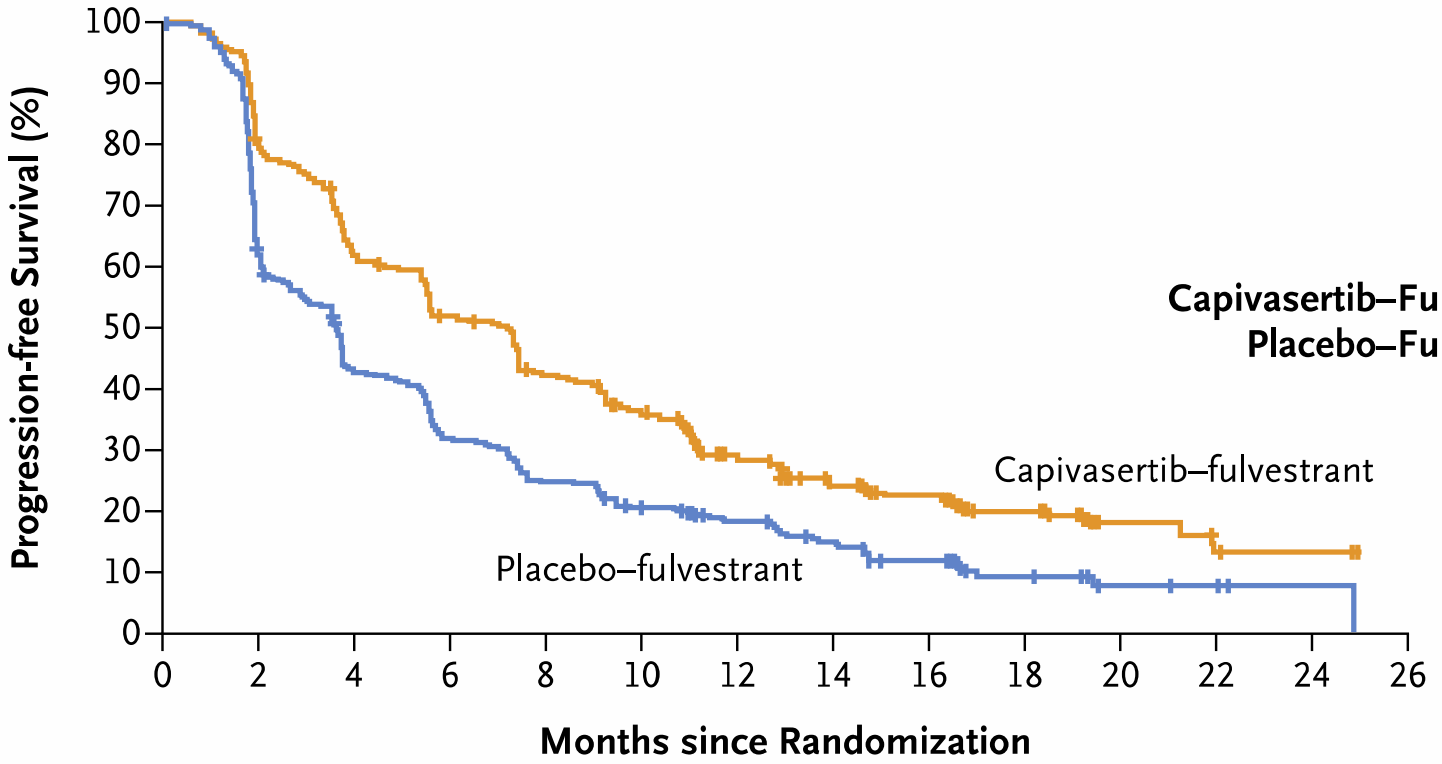
Objective response rate
- Overall
- AKT pathway-altered tumors

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

Turner NC et al SABCS 2022 and NEJM 2023

CAPItello-291: Capivasertib for HR+ MBC, PFS

A Overall Population



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Capivasertib–Fulvestrant	355	258	7.2 (5.5–7.4)
Placebo–Fulvestrant	353	293	3.6 (2.8–3.7)

Adjusted hazard ratio for disease progression or death, 0.60 (95% CI, 0.51–0.71)
P<0.001

No. at Risk

Capivasertib–fulvestrant	355	266	207	172	138	115	78	55	43	25	8	5	2	0
Placebo–fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

Turner NC et al NEJM 2023

DESTINY-Breast06: T-DXd in Chemo-Naïve HR+ MBC

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC

  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i

    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

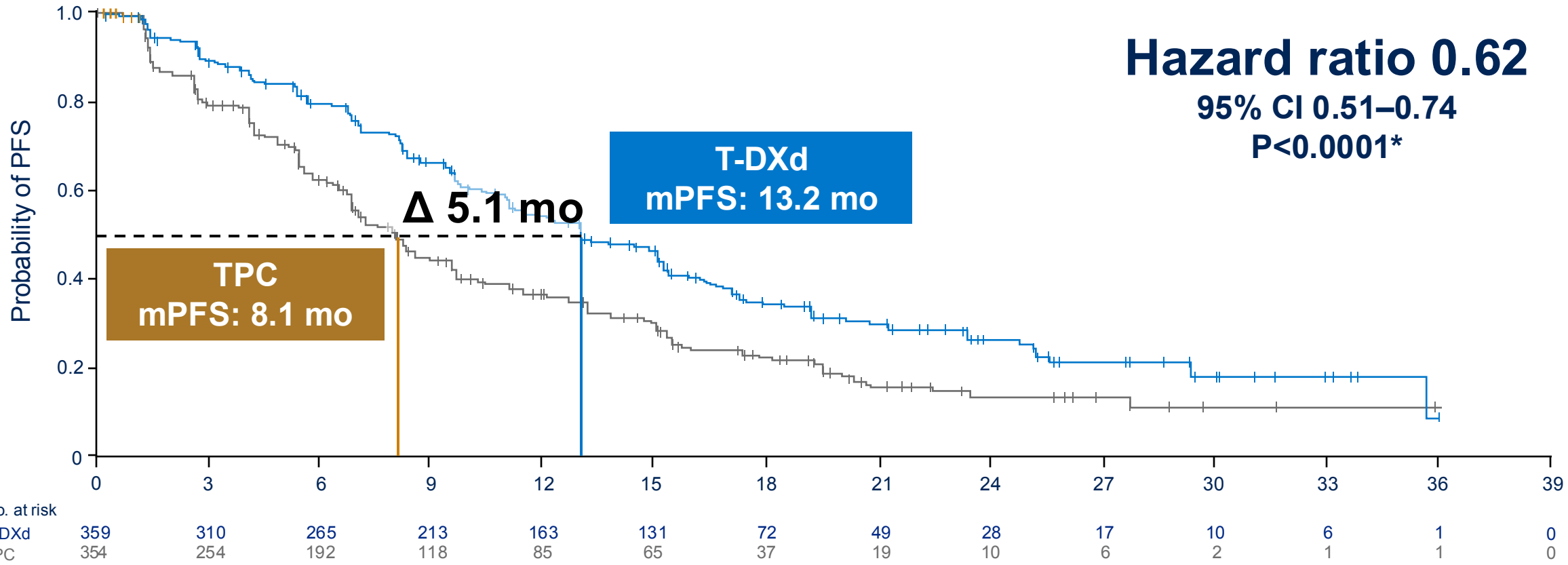
- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

Curigliano G et al ASCO 2024

DB-06: PFS (BICR) in HER2-low primary endpoint



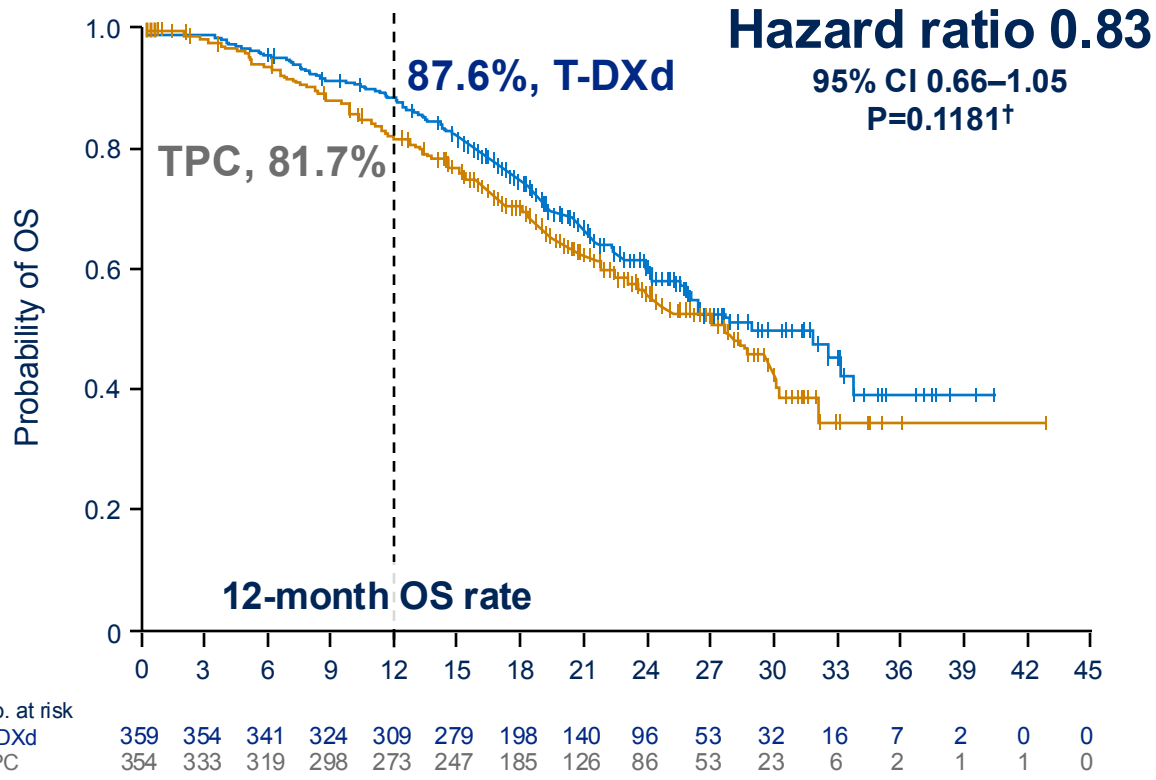
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Bardia A et al. *N Engl J Med* 2024 Sep 15;Online ahead of print
Curigliano G et al ASCO 2024

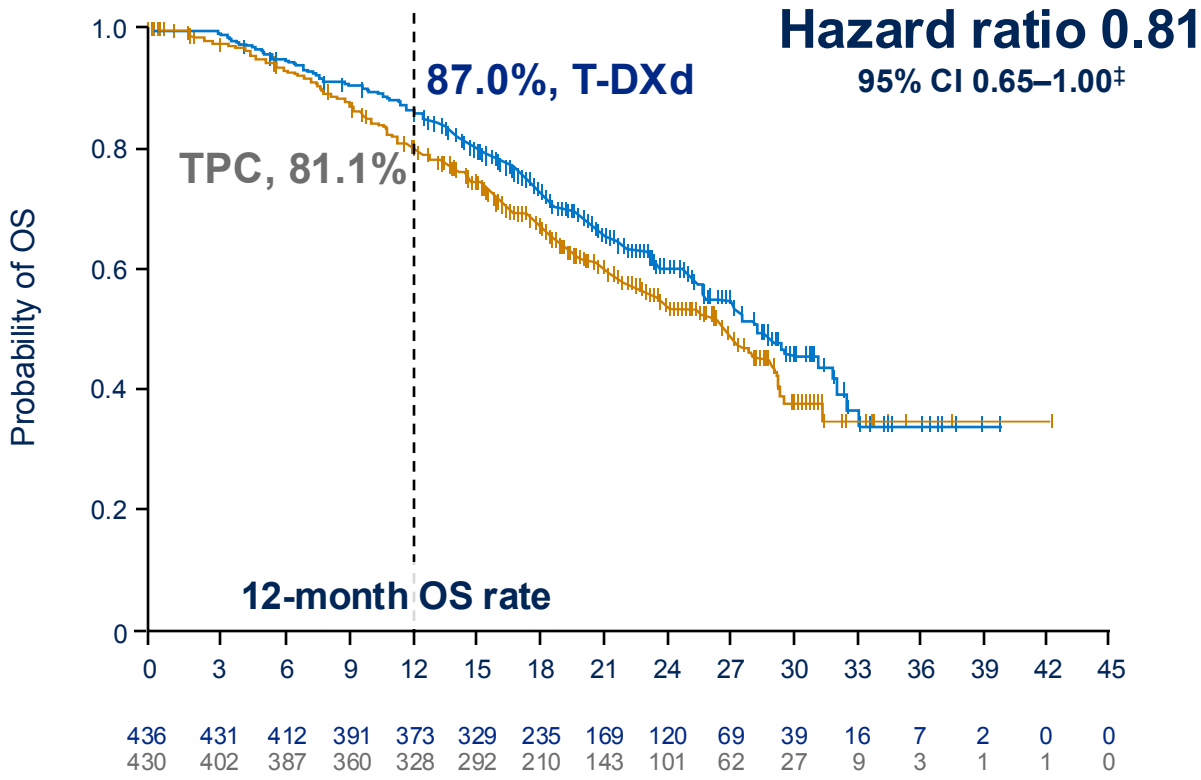
DB-6: OS in HER2-low and ITT

HER2-low*



20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

ITT (HER2-low + HER2-ultralow)



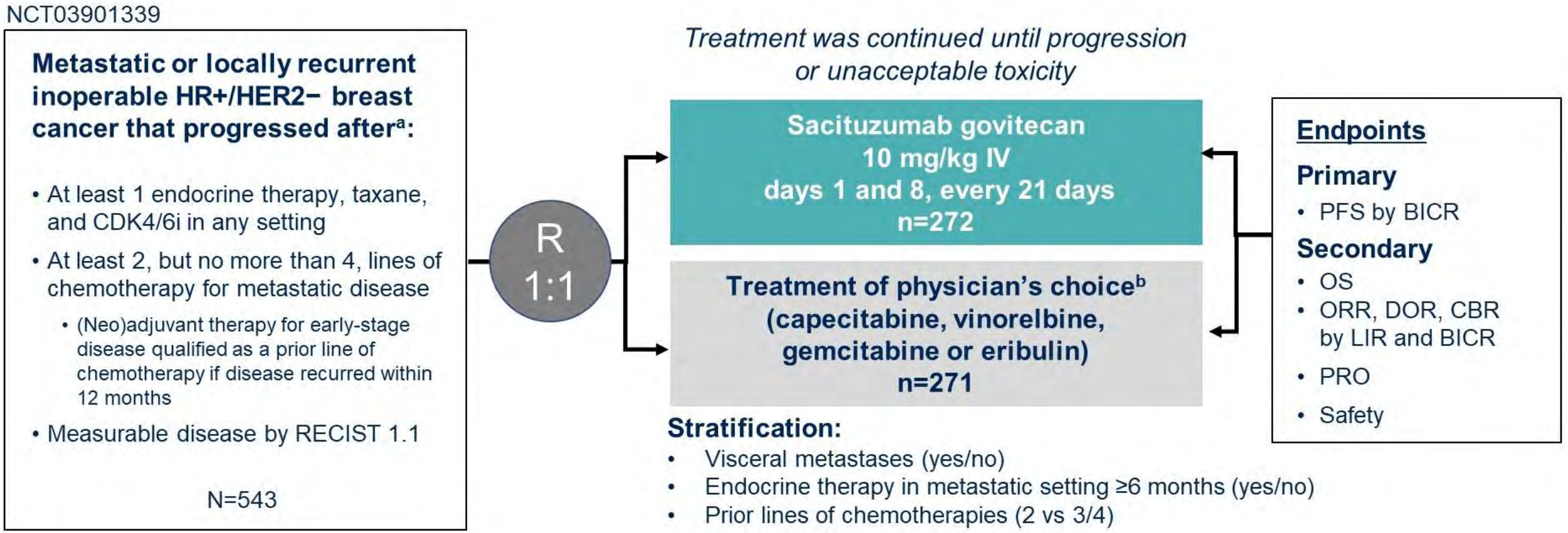
17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

*39.6% maturity (of total N for population) at this first interim analysis. Median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure. Median duration of follow up was 18.2 months (ITT)

CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intent-to-treat; mo, months; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

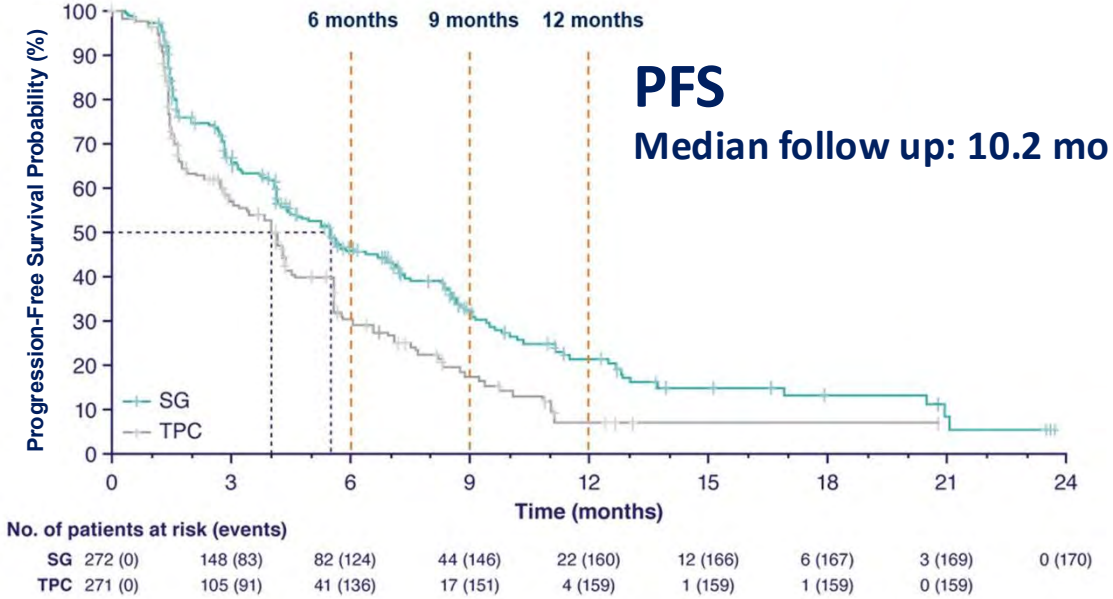
Curigliano G et al ASCO 2024

TROPiCS-02: Sacituzumab Govitecan in HR+/HER2- MBC



Rugo HS, et al. J Clin Oncol. 2022
Rugo HS, et al. ASCO 2022. Abstract LBA 1001

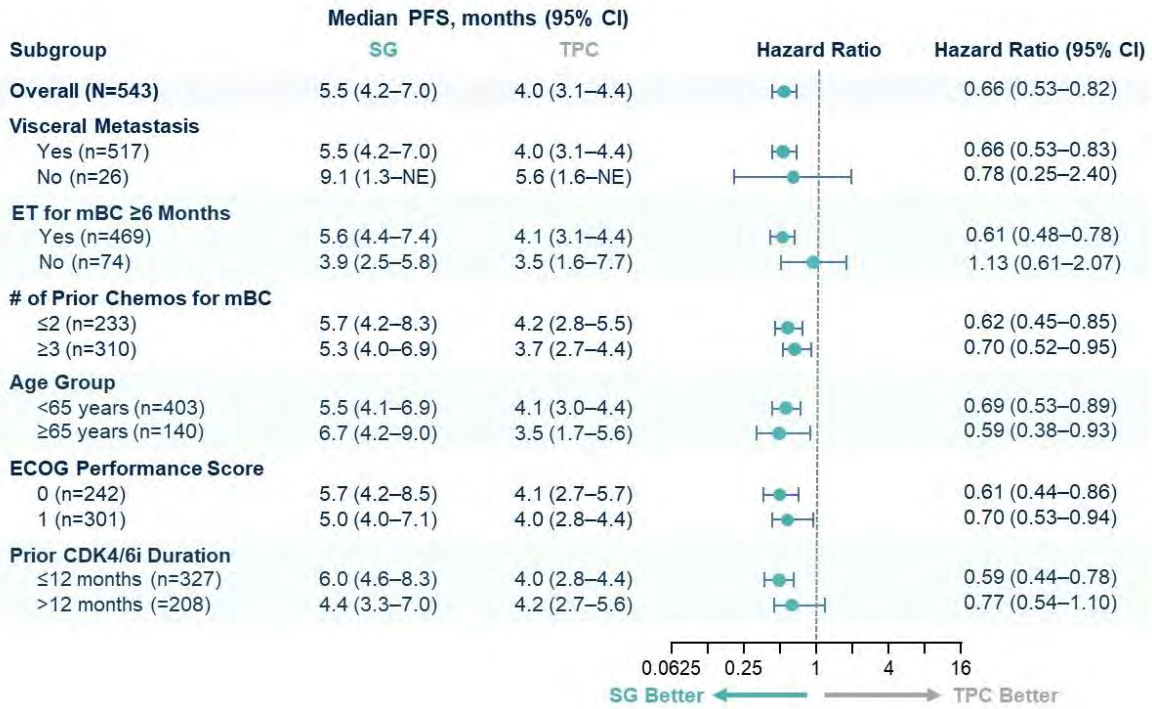
TROPiCS-02: Clinical Outcomes



PFS

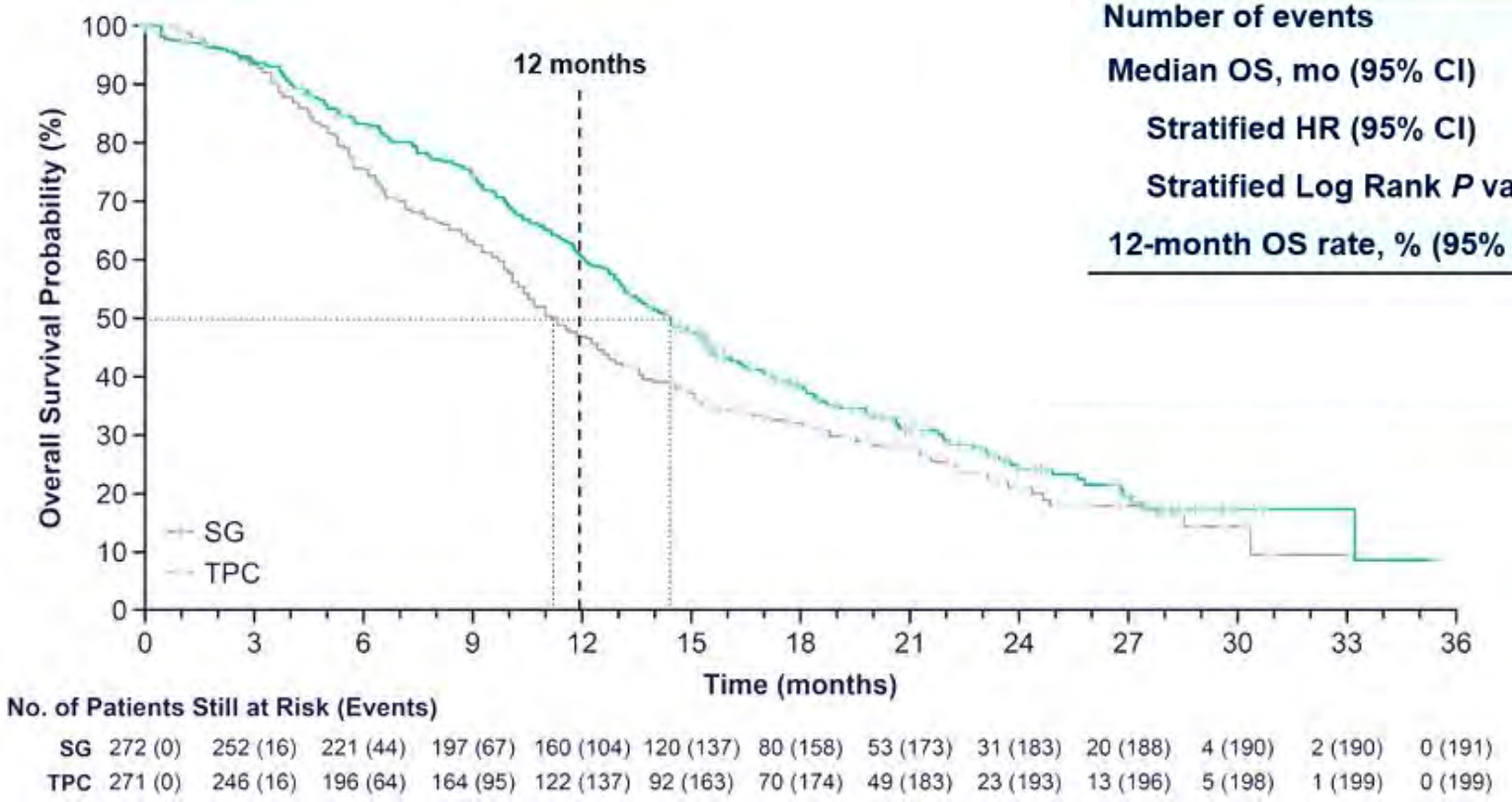
Median follow up: 10.2 mo

BICR 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)



Rugo HS, et al. J Clin Oncol. 2022
Rugo HS, et al. ASCO 2022. Abstract LBA 1001

TROPiCS-02: Clinical Outcomes



	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)

OS benefit for SG vs TPC was generally consistent across predefined subgroups, including pts with:

- ≥ 3 prior chemotherapy regimens in the metastatic setting
- Visceral metastases
- Prior ET in the metastatic setting for ≥ 6 mo

Rugo HS, et al. Lancet 2023 Oct 21;402(10411):1423-33
Rugo HS, et al. ESMO 2022. Abstract LBA76

TROPION-Breast01 Study Design[1]

Randomized, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

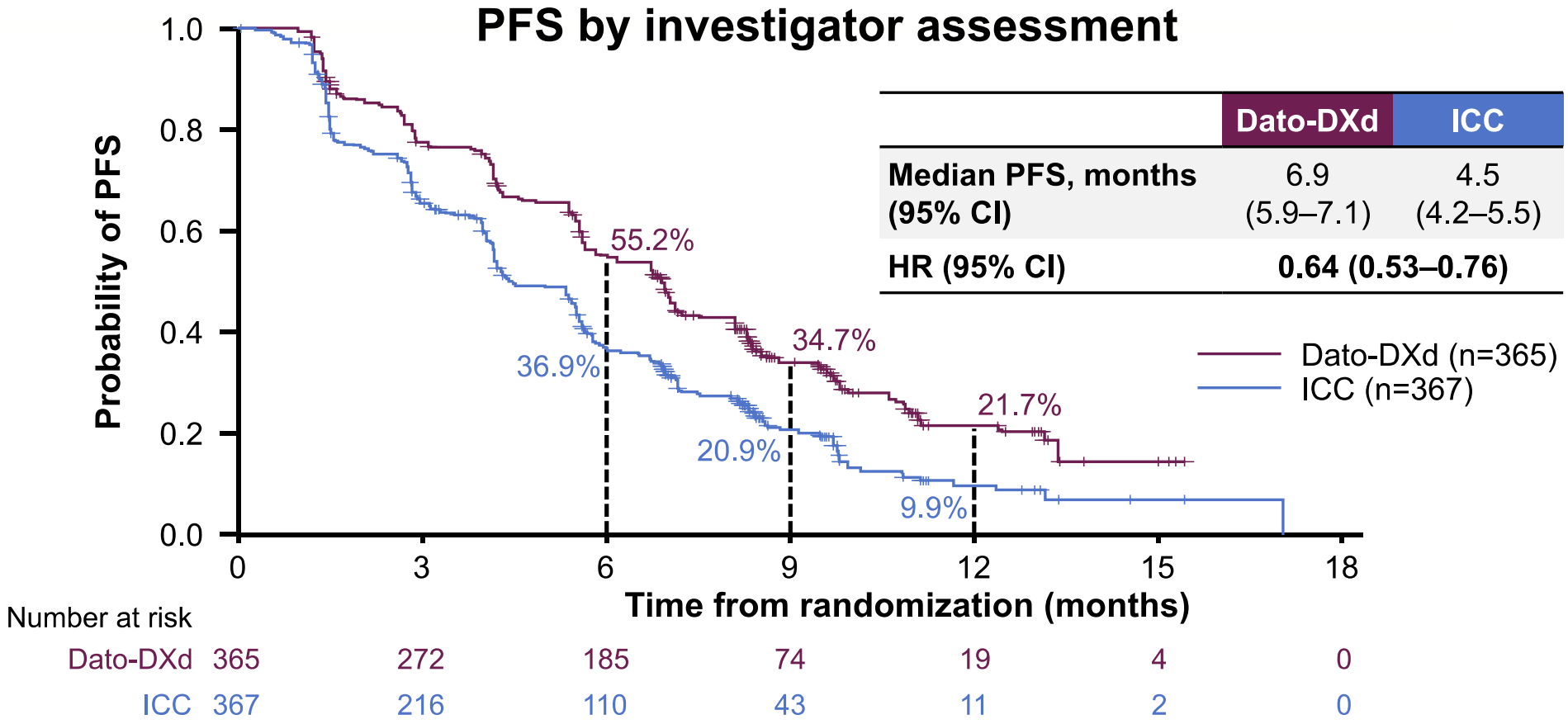
Randomization stratified by:
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice). CDK4/6, cyclin-dependent kinase 4/6; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; PD, progressive disease; PROs, patient-reported outcomes; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TFST, time to first subsequent therapy.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	**0.64 (0.53–0.76)**	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Data cut-off: 17 July 2023.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

Bardia A et al. J Clin Oncol 2024 Sep 12;Online ahead of print
Bardia A et al SABCS 2023

Overall Safety Summary

TRAEs, n (%)[1]	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

- Most common TRAEs leading to dose interruption:
  - Dato-DXd: fatigue*, infusion-related reaction, ILD, stomatitis (each 1%)
  - ICC: neutropenia† (17%), leukopenia‡ (3%)
- No TRAEs led to discontinuation in ≥1% of patients in either arm
- One treatment-related death in the ICC arm due to febrile neutropenia

*Fatigue includes the preferred terms of fatigue, asthenia, and malaise. †Neutropenia includes the preferred terms neutropenia and neutrophil count decreased.
‡Leukopenia includes the preferred terms of white blood cell count decreased and leukopenia.
ILD, interstitial lung disease; TRAEs, treatment-related adverse events.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

Metastatic Breast Cancer: Case Summary and Approach

45 yo > de novo metastatic HR+/HER2- breast cancer with bone involvement

1st Line::
AI/OS + CDK4/6i
(Ribociclib)

Fulvestrant + Palbo
+ Inavolisib
(PIK3CAm,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib

Fulvestrant + Alpelisib
(PIK3CAm)

Fulvestrant + Capivasertib
(PIK3CAm, AKTm, PTENm)

Elacestrant
(ESR1m)

Olaparib
(BRCAm)

NGS
ctDNA at
progression

3rd Line (and beyond)::
Antiestrogen + Everolimus

Trastuzumab Deruxtecan (ADC, HER2-low)

Chemotherapy (many choices)

Sacituzumab Govitecan (ADC)

**Ongoing clinical trials exploring:
New antiestrogens
New CDK4/2 inhibitors
New targeted agents (PI3K, RAS pathway)
New ADCs

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

Agenda

Module 1 — HR-Positive Breast Cancer: *Drs O'Shaughnessy and Wander*

Module 2 — Prostate Cancer: *Drs M Smith and Srinivas*

Module 3 — Lung Cancer: *Drs Goldberg and Sabari*

Module 4 — Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia: *Drs Kahl and S Smith*

Module 5 — Multiple Myeloma: *Drs Lonial and Raje*

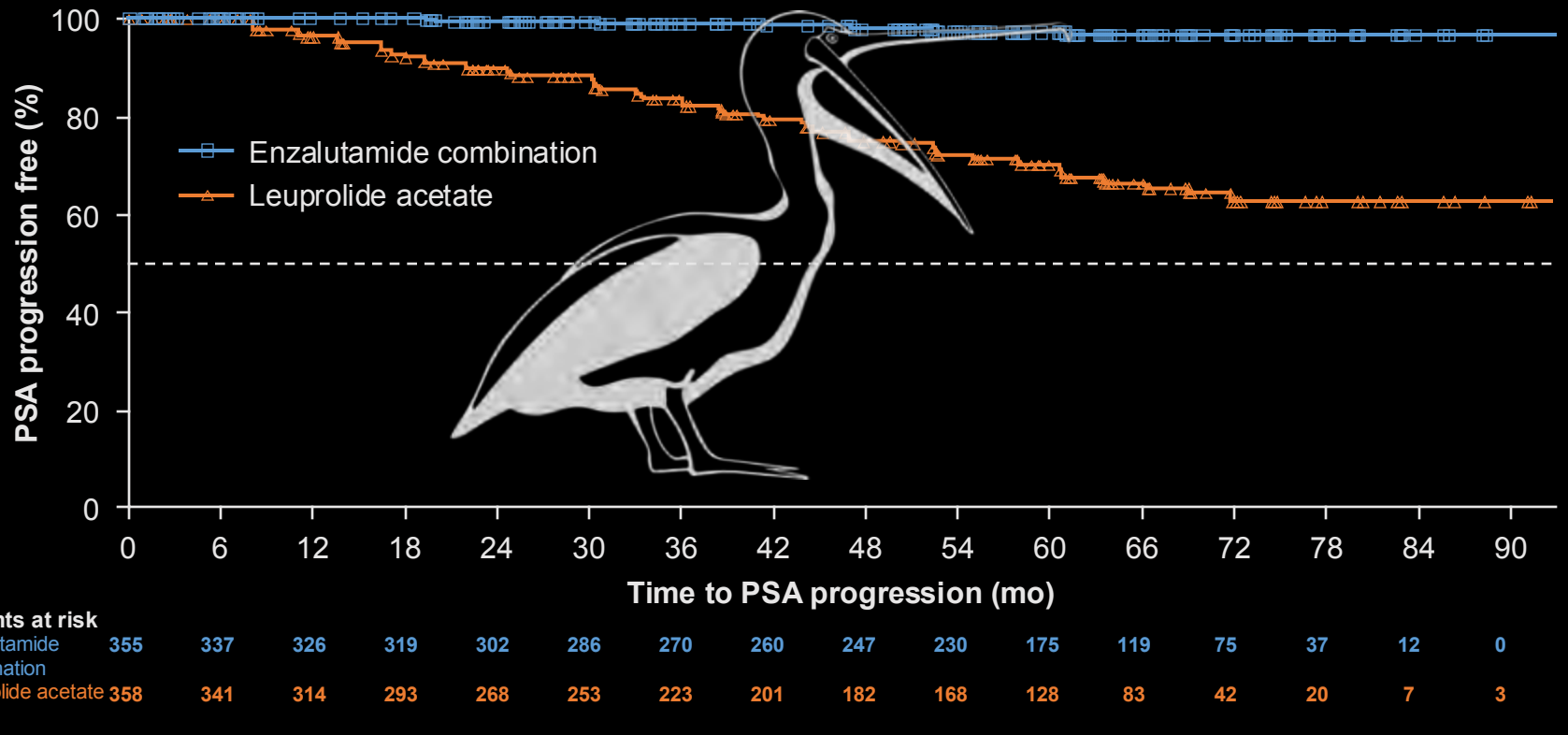
Prostate Cancer Faculty

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

Sandy Srinivas, MD
Professor of Oncology
Clinical Research Leader, GU Oncology
Stanford University
Stanford, California

RTP
RESEARCH TO PRACTICE

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.

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

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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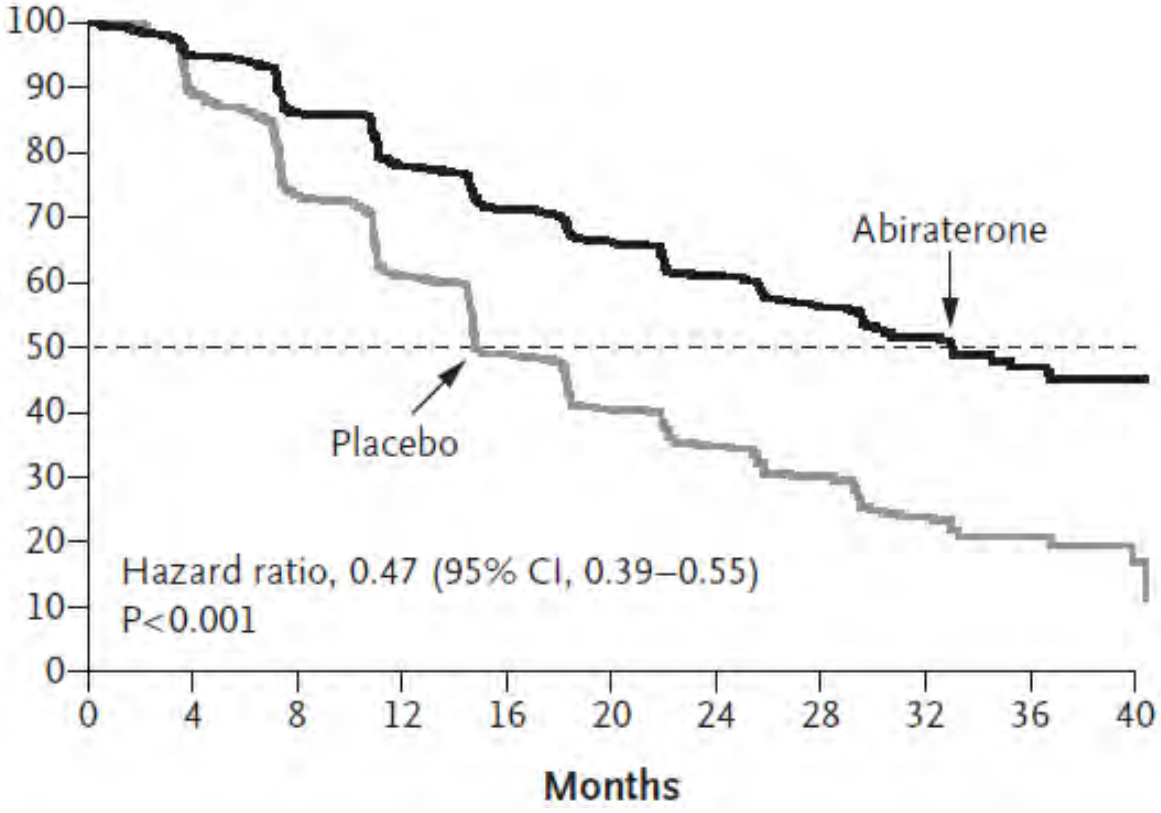
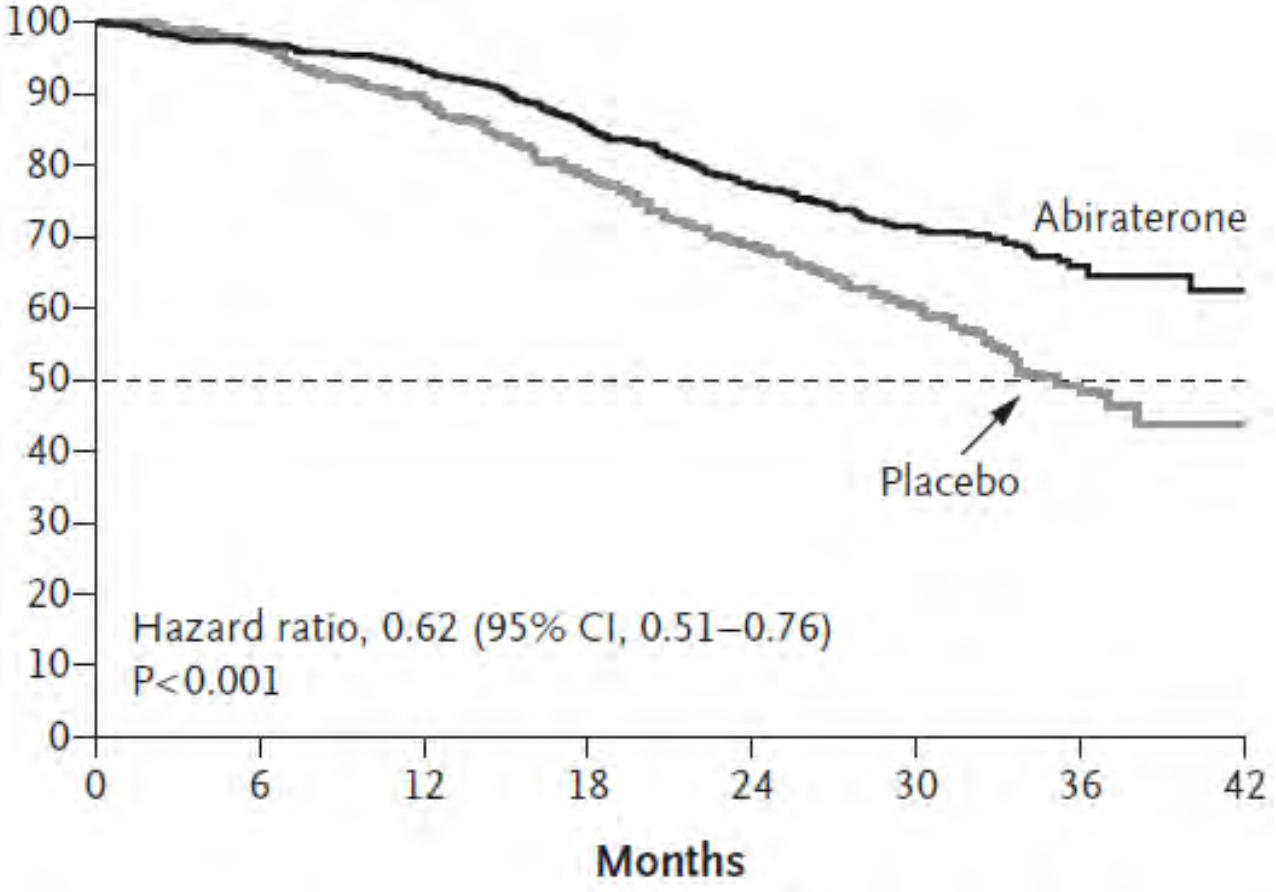
LATITUDE: Abiraterone Acetate for mCSPC

Radiographic Progression-Free Survival



Overall Survival



Fizazi et al (2017) *N Engl J Med 377*: 352-60

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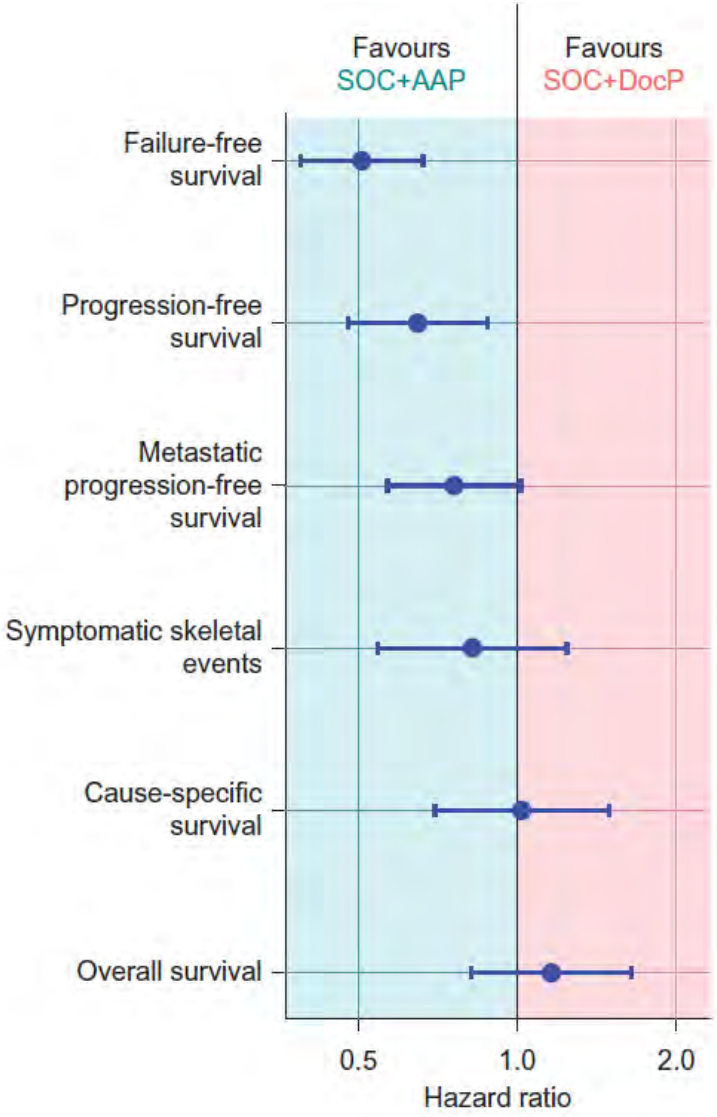
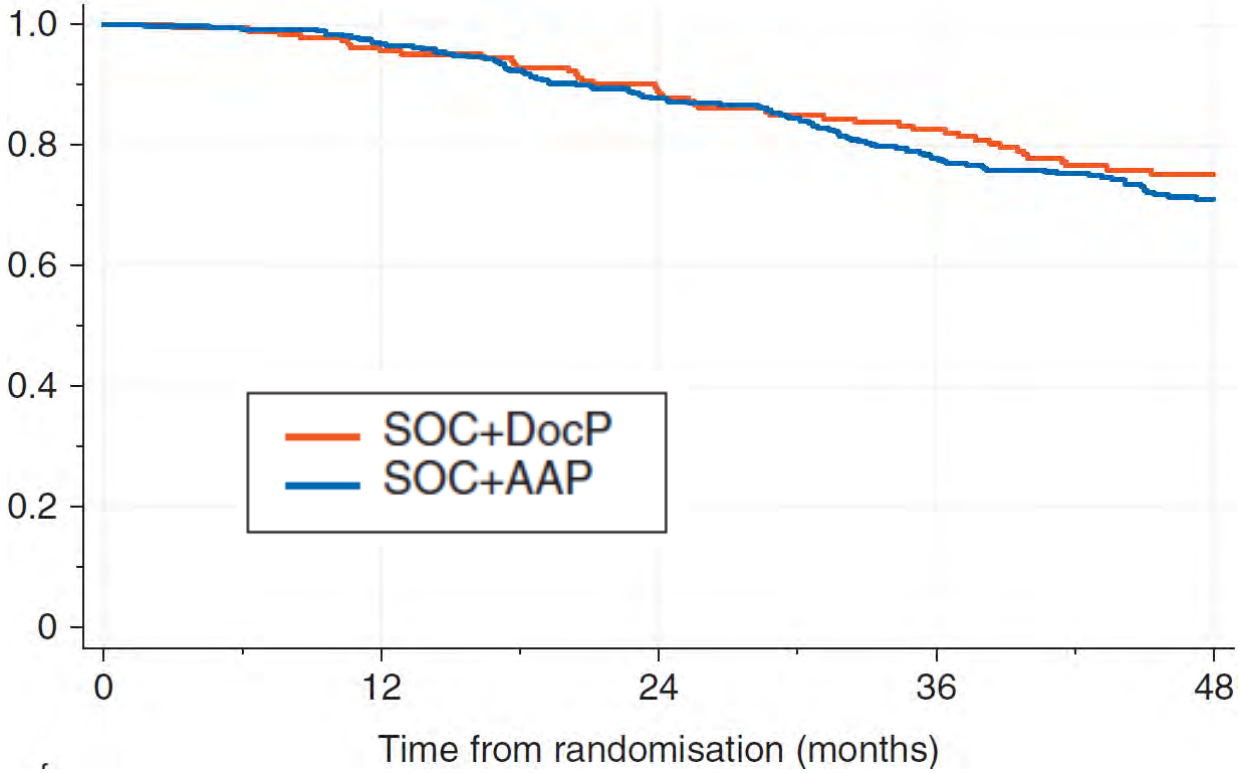
STAMPEDE: Docetaxel vs Abiraterone Comparison



Overall Survival



Sydes et al (2018) *Annals of Oncology* 29:1235-1248

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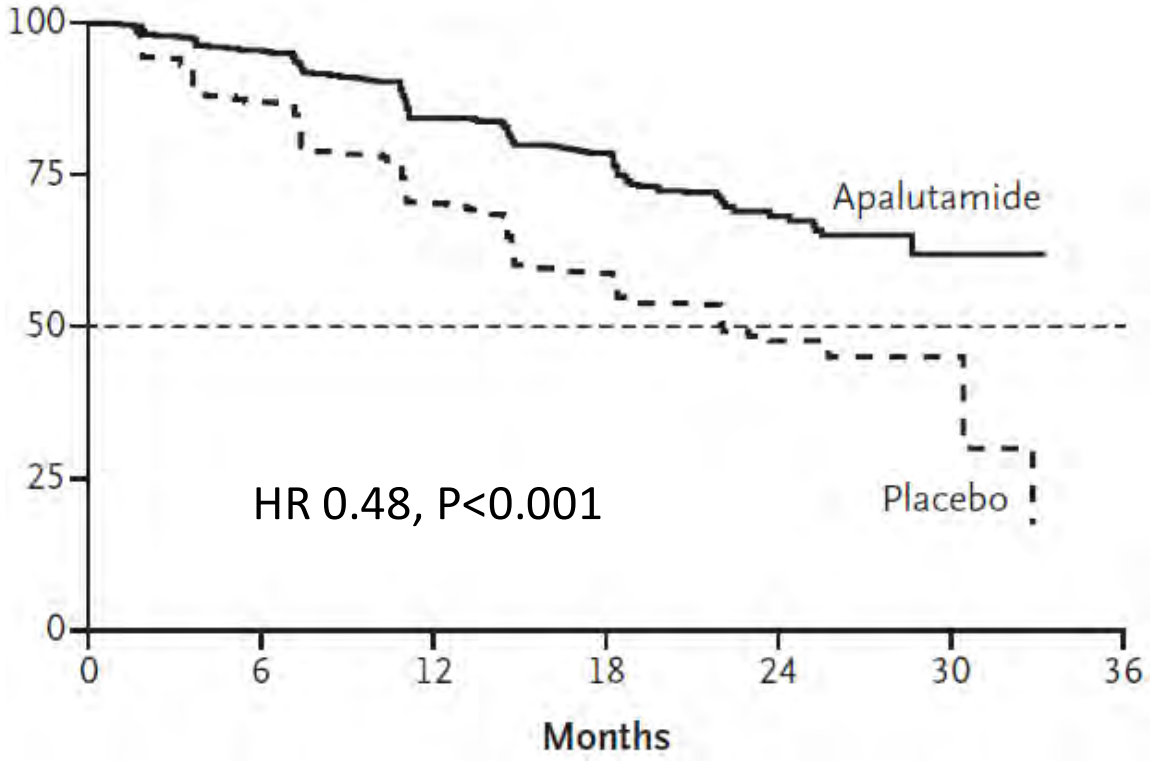
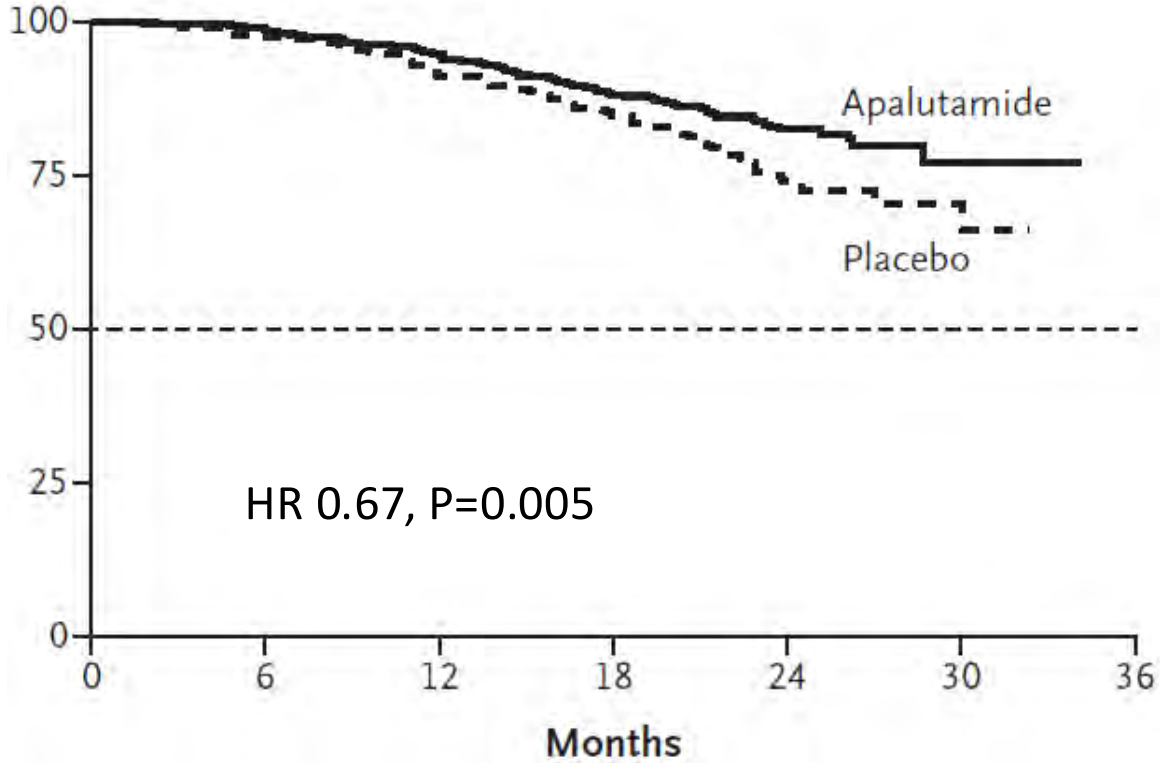
TITAN: Apalutamide for mCSPC

Radiographic Progression-Free Survival



Overall Survival

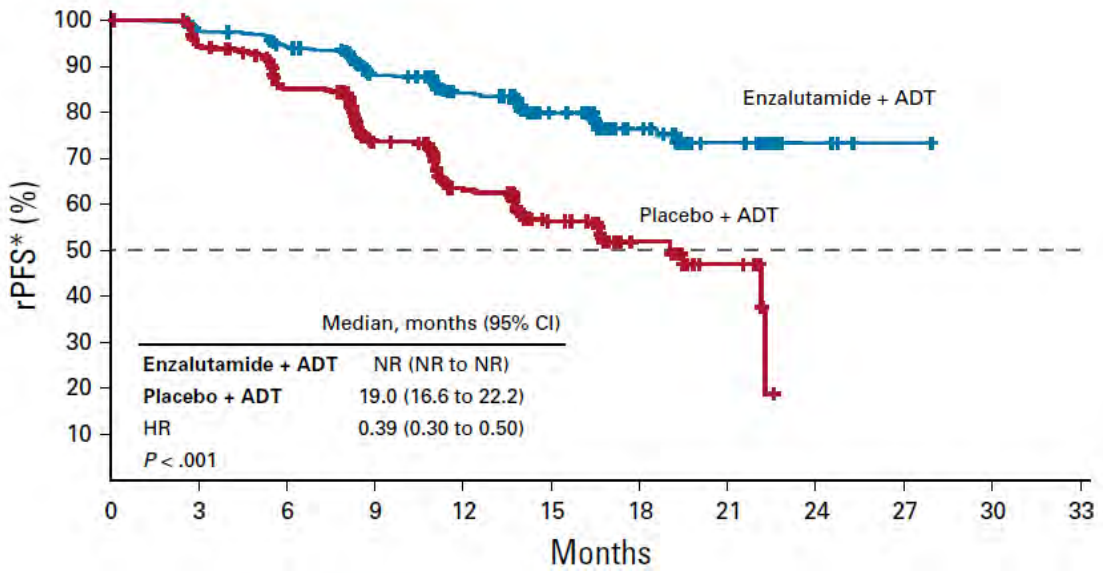


Chi et al (2019) *N Engl J Med 381*: 13-24

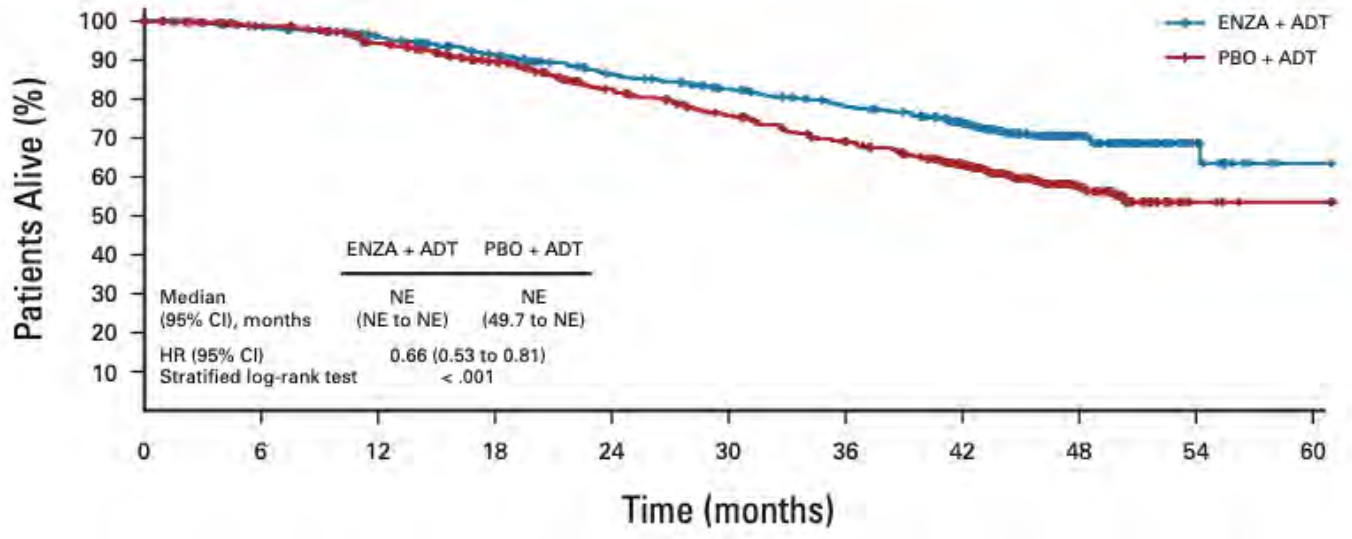
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ARCHES: Enzalutamide for mCSPC

rPFS



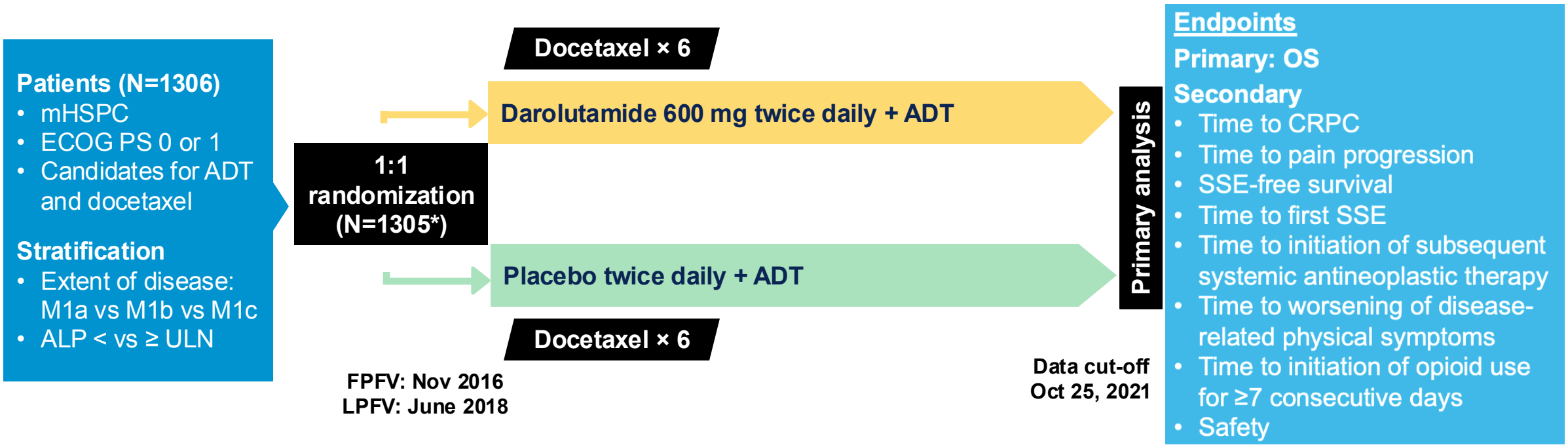
OS



Armstrong et al (2019) *J Clin Oncol* 37(32)*:* 2974-2986; Armstrong et al (2022) *J Clin Oncol* 2022 40(15):1616-1622.

ARASENS Study Design

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



- 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* 2022;386:1132-1142

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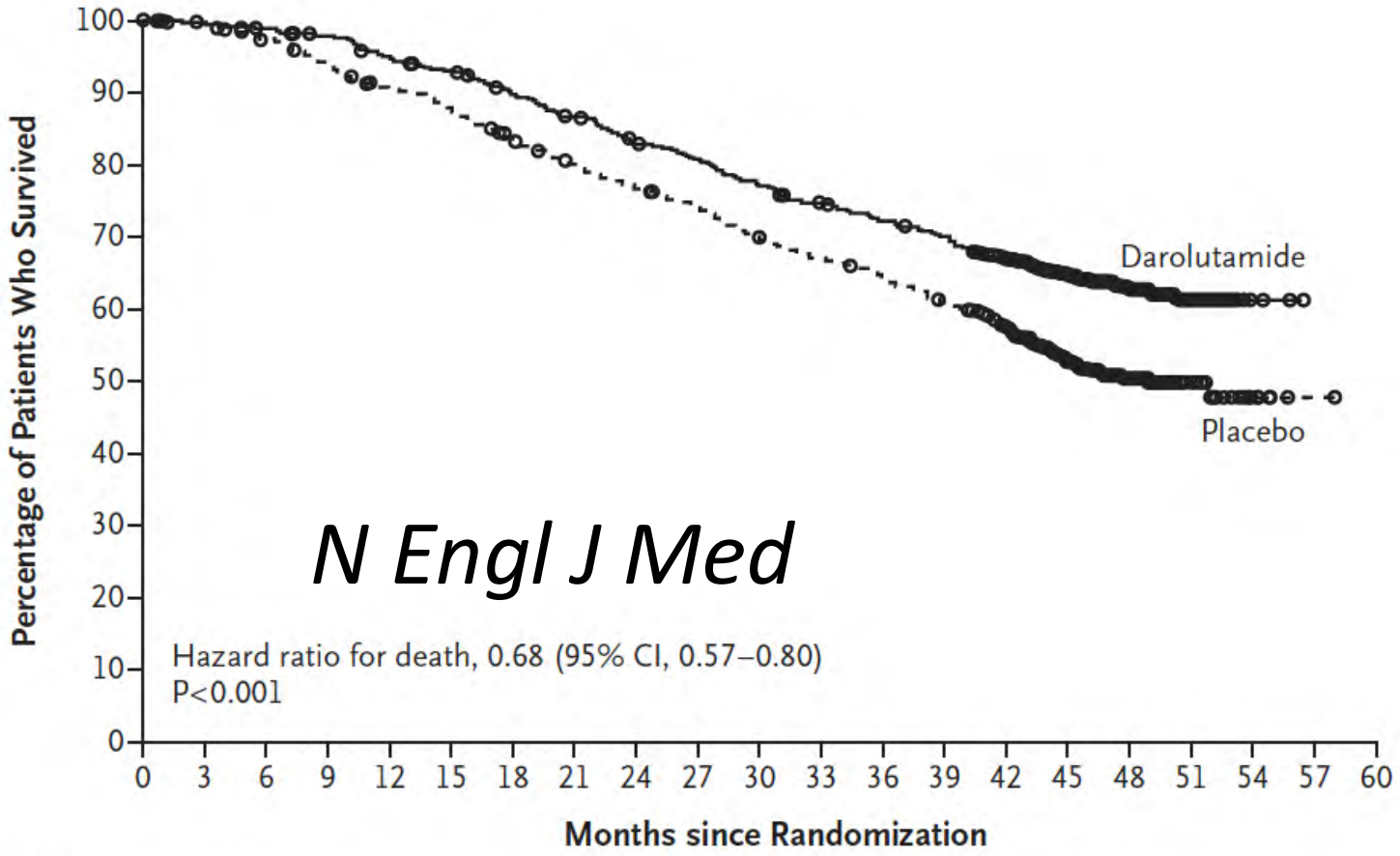
ARASENS Primary Endpoint: Overall Survival



N Engl J Med

	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* 2022;386:1132-1142

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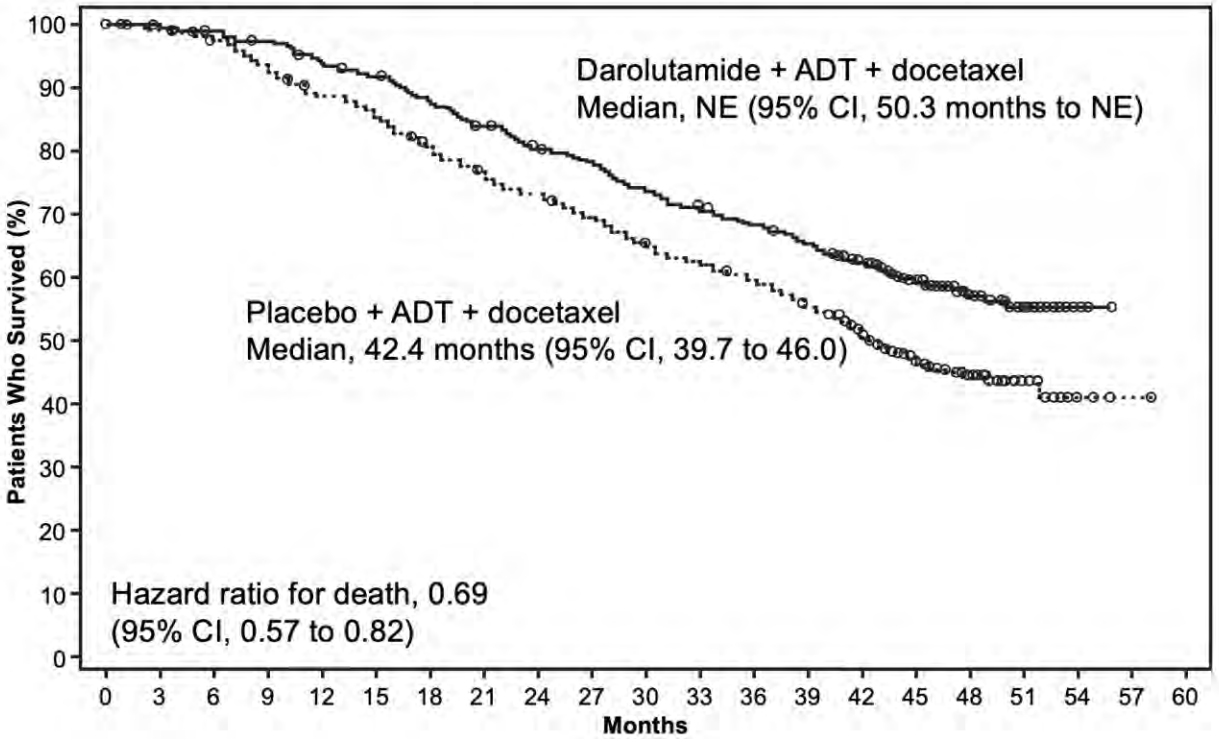
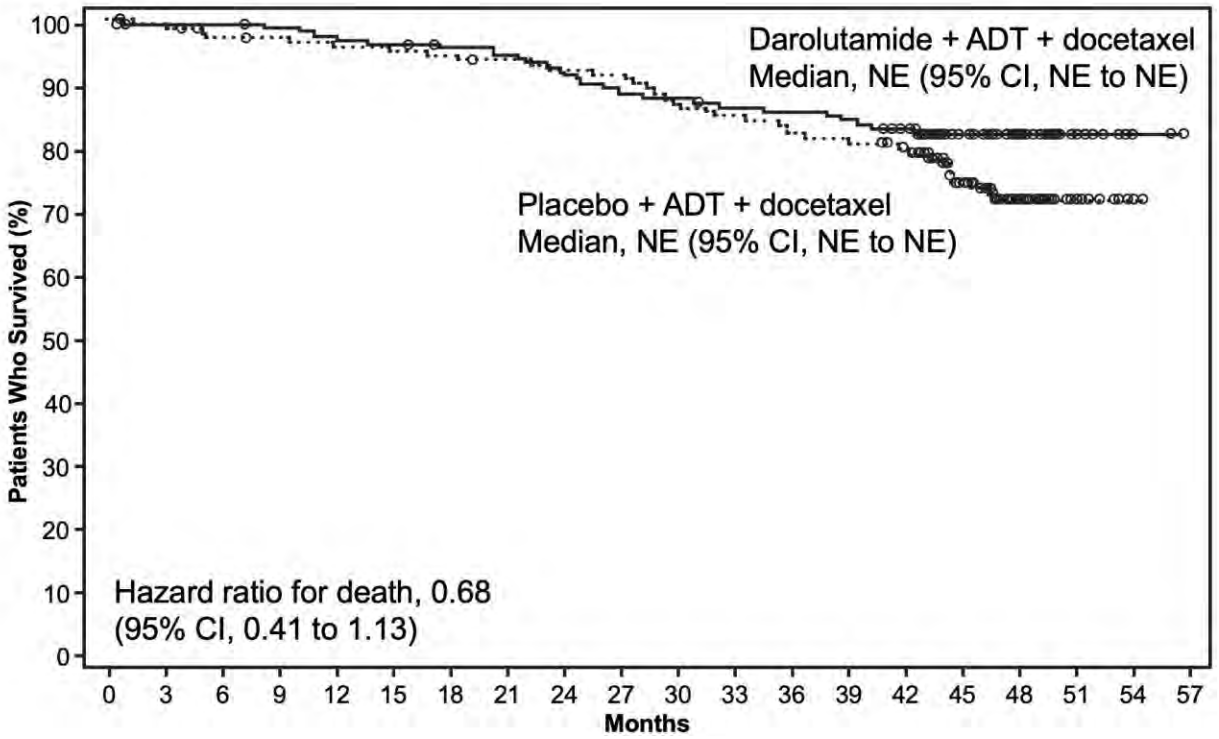
ARASENS: Overall Survival by Disease Volume

High-Volume Metastatic Disease



Low-Volume Metastatic Disease



Hussain et al (2023) *J Clin Oncol* **41**, 3595-3607(2023).

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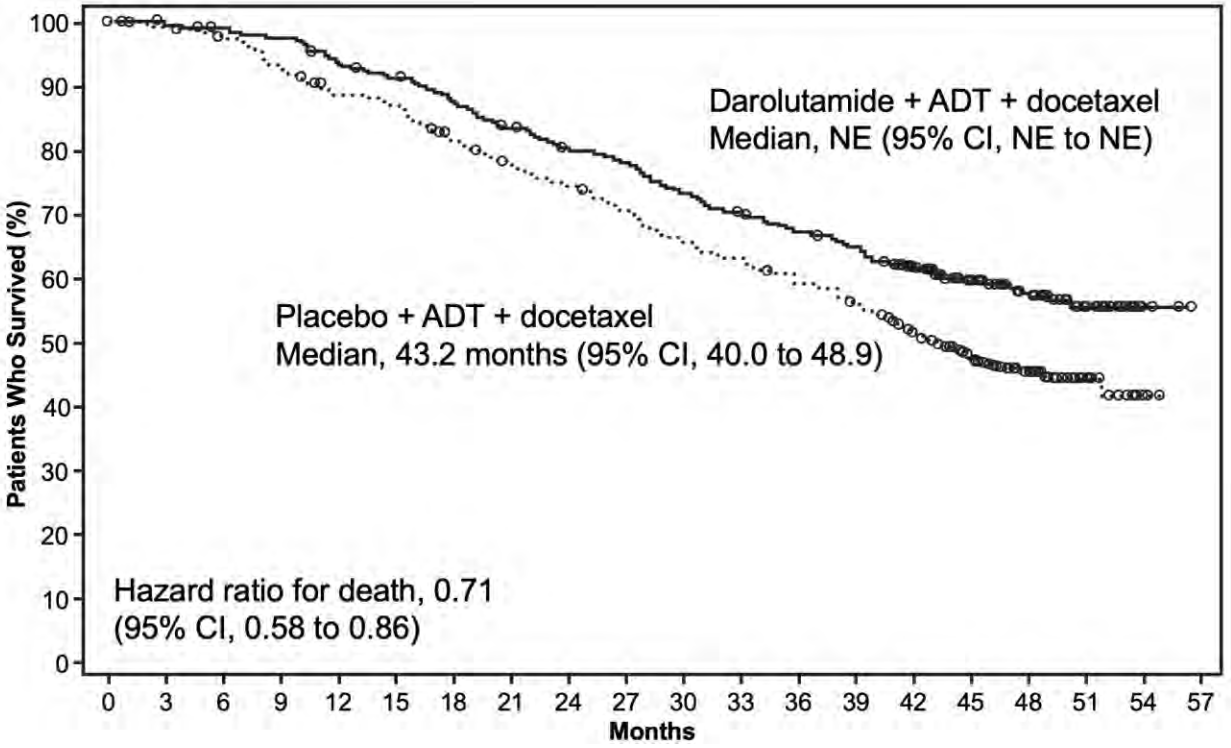
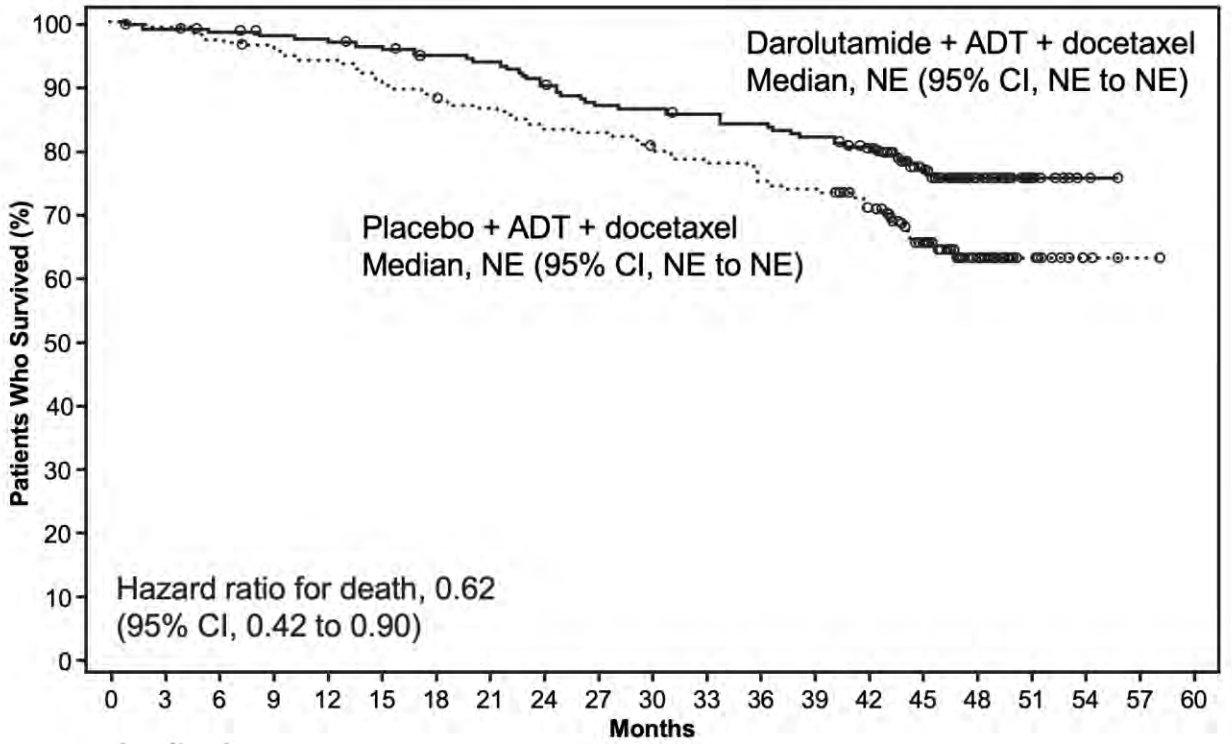
ARASENS: Overall Survival by Risk Group

High-Risk Group



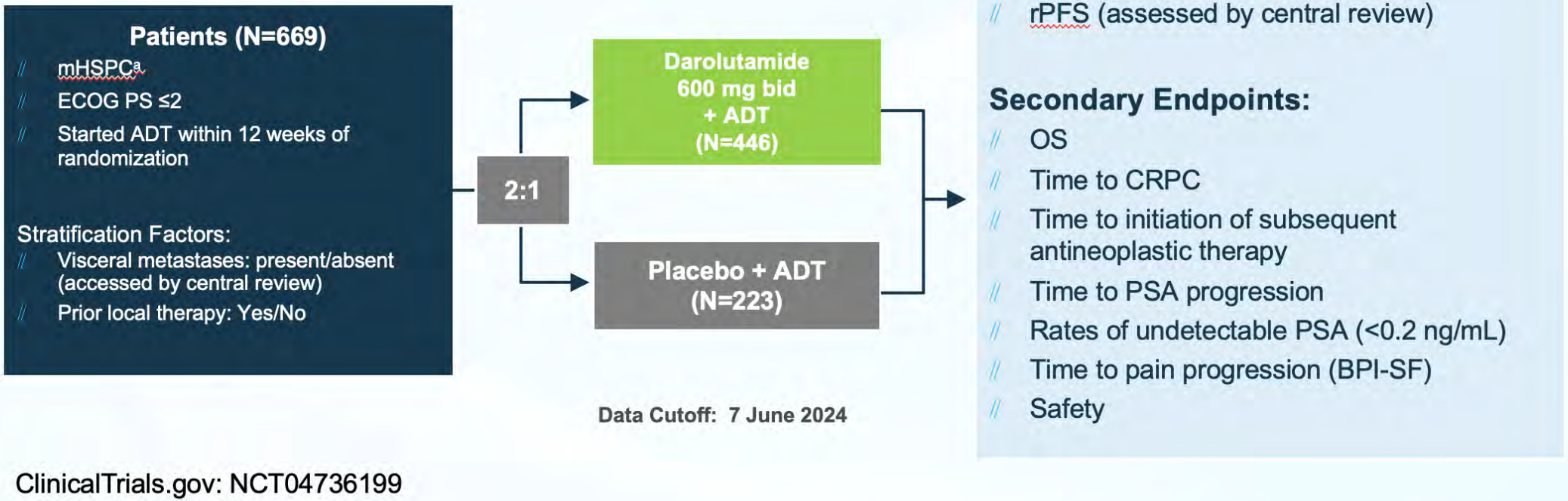
Low-Risk Group



Hussain et al (2023) *J Clin Oncol* **41**, 3595-3607(2023).

ARANOTE Study Design

A randomized, double-blind, placebo-controlled phase 3 study

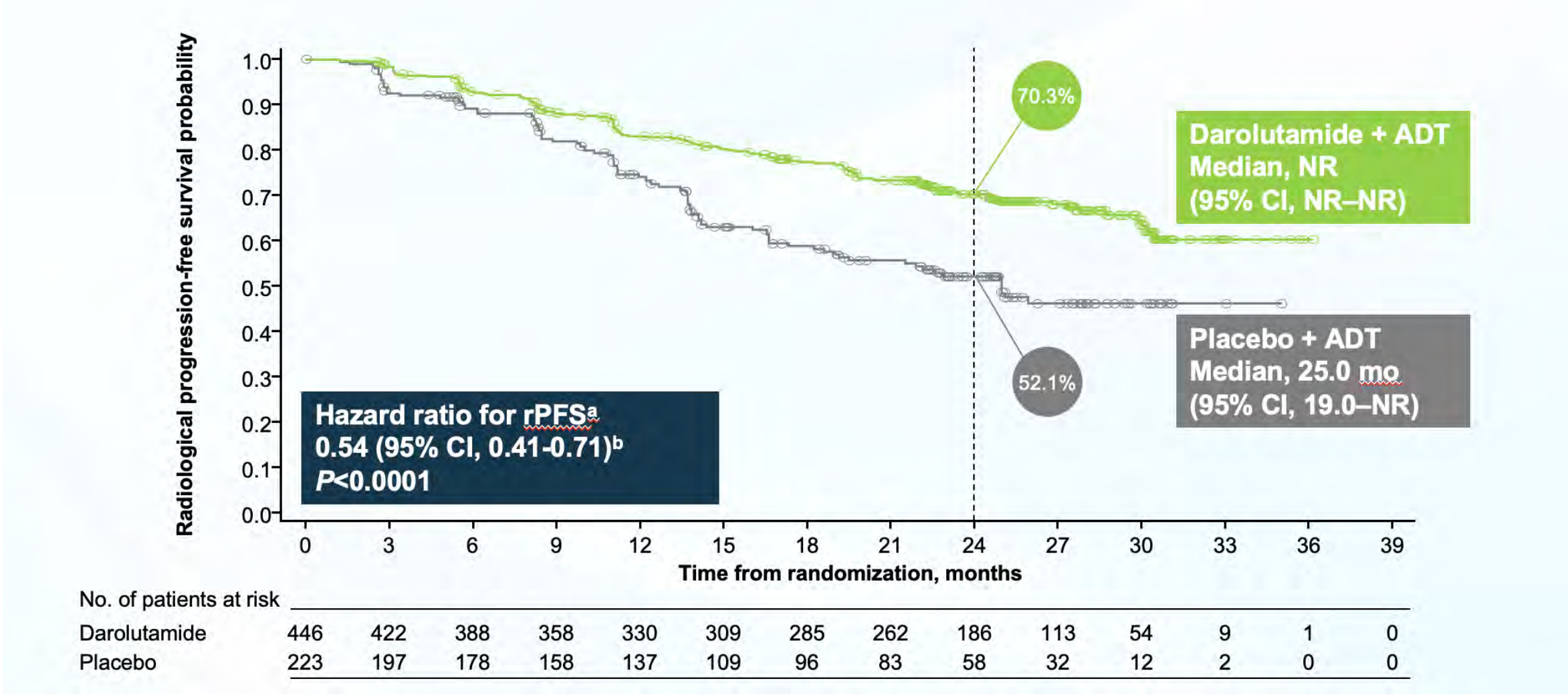


ClinicalTrials.gov: NCT04736199

[a]Metastatic disease confirmed by conventional imaging method either by a positive ^{99}mTc-phosphonate bone scan, or soft tissue or visceral metastases, either by contrast-enhanced abdominal/pelvic/chest CT or MRI scan assessed by central review.
ADT, androgen deprivation therapy; bid, twice a day; AE, adverse event; BPI-SF, Brief Pain Inventory-Short Form; CRPC, castration-resistant prostate cancer; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate specific antigen; rPFS, radiological progression-free survival.
1. Clinicaltrials.gov identifier: NCT04736199. Accessed September 2024. https://clinicaltrials.gov/ct2/show/NCT04736199. 2. Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

Saad et al (2024) *J Clin Oncol* **0**, JCO-24-01798

ARANOTE Primary Endpoint: rPFS



Saad et al (2024) *J Clin Oncol* **0**, JCO-24-01798

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

Week 37

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:
- PROs
- 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; PROs, patient-reported outcomes; PSA, prostate-specific antigen; PSADT, PSA doubling time; q, every; R, randomization; RP, radical prostatectomy; w, weeks.

Freedland et al (2023) *N Engl J Med* 2023;389:1453-1465

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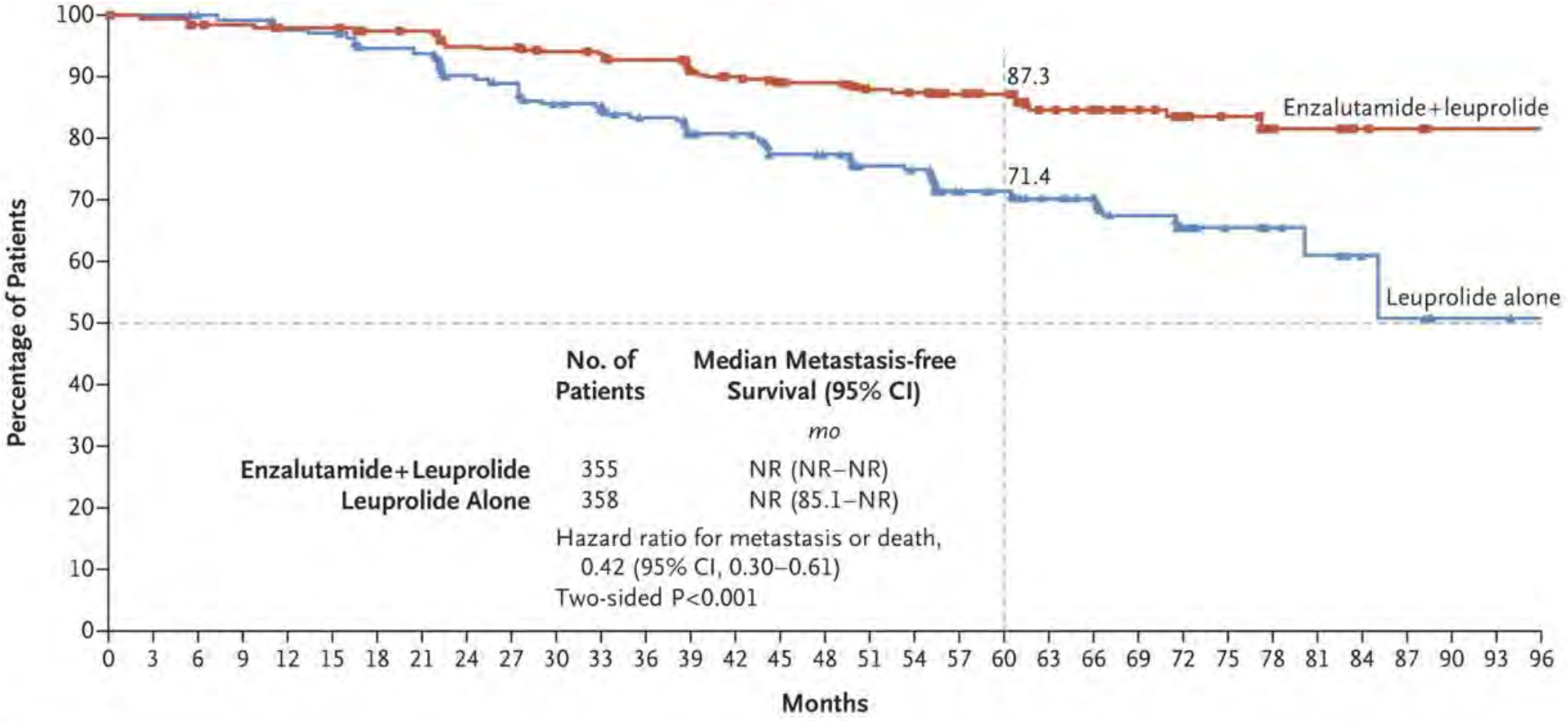
EMBARK Primary Endpoint:
MFS for Enzalutamide Combination vs. Leuprolide



No. at Risk

Enzalutamide+ leuprolide	355	339	331	330	324	324	318	317	304	303	292	290	281	270	265	252	251	236	234	183	180	119	116	83	60	51	24	22	6	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

Freedland et al (2023) *N Engl J Med* 2023;389:1453-1465

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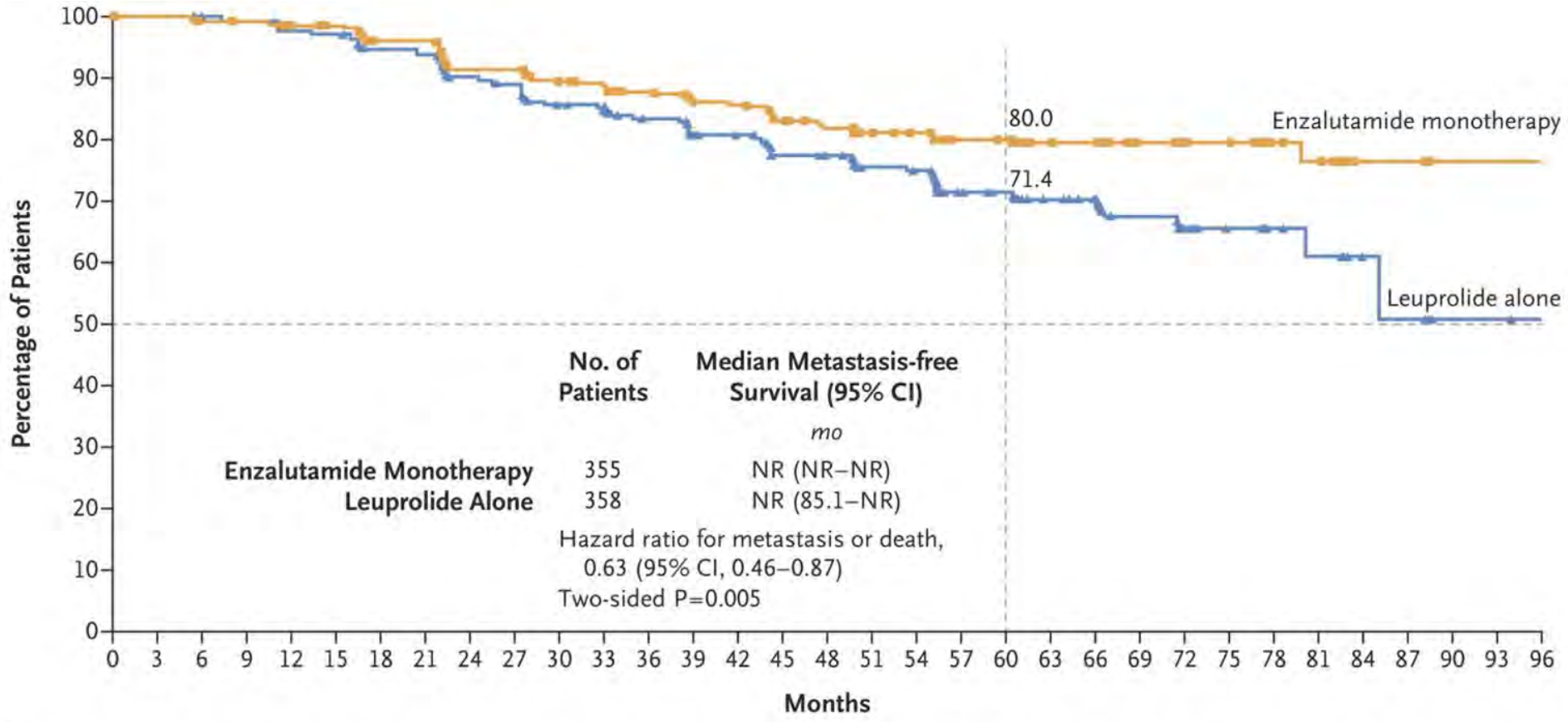
EMBARK Key Secondary Endpoint: MFS for Enzalutamide Monotherapy vs. Leuprolide



No. at Risk

Enzalutamide monotherapy	355	350	342	341	328	326	309	309	287	287	273	269	260	248	247	235	228	211	209	172	171	109	108	76	52	49	26	24	5	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

Freedland et al (2023) *N Engl J Med* 2023;389:1453-1465

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Phase III EMBARK Trial: Common Adverse Events

Event	Enzalutamide + Leuprolide (N = 353)		Leuprolide Alone (N = 354)		Enzalutamide Monotherapy (N = 354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Most common adverse events‡						
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)	7 (2.0)	75 (21.2)	1 (0.3)	81 (22.9)	2 (0.6)
Hypertension	82 (23.2)	24 (6.8)	69 (19.5)	18 (5.1)	67 (18.9)	19 (5.4)
Fall	74 (21.0)	4 (1.1)	51 (14.4)	4 (1.1)	56 (15.8)	7 (2.0)
Back pain	60 (17.0)	3 (0.8)	54 (15.3)	1 (0.3)	62 (17.5)	3 (0.8)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	1 (0.3)
Constipation	46 (13.0)	1 (0.3)	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	8 (2.3)	44 (12.4)	4 (1.1)	45 (12.7)	9 (2.5)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	1 (0.3)	29 (8.2)	1 (0.3)	54 (15.3)	2 (0.6)
Pain in arm or leg	41 (11.6)	3 (0.8)	36 (10.2)	2 (0.6)	40 (11.3)	1 (0.3)
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	2 (0.6)	37 (10.5)	2 (0.6)	41 (11.6)	3 (0.8)
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	4 (1.1)	28 (7.9)	3 (0.8)	36 (10.2)	6 (1.7)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)§	3 (0.8)
Coronavirus disease 2019	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	2 (0.6)
Peripheral edema	27 (7.6)	1 (0.3)	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	7 (2.0)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

Freedland et al. *N Engl J Med* 2023;389:1453-65.

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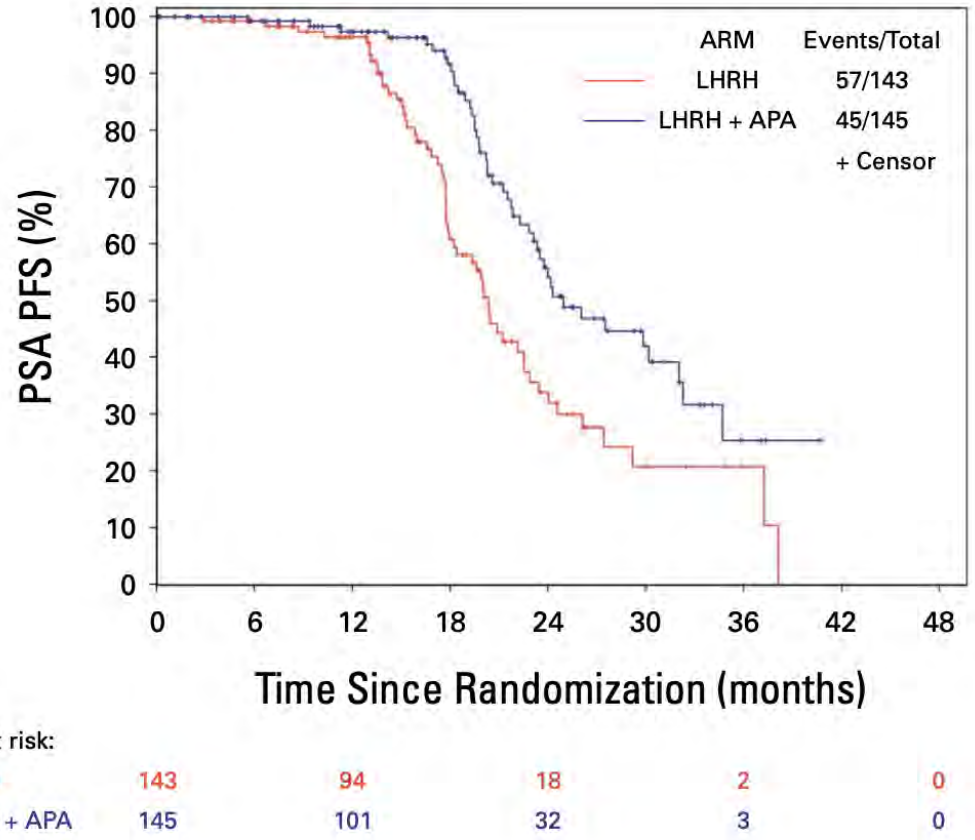
PRESTO: Treatment Intensification in nmCSPC

ADT vs ADT + apalutamide

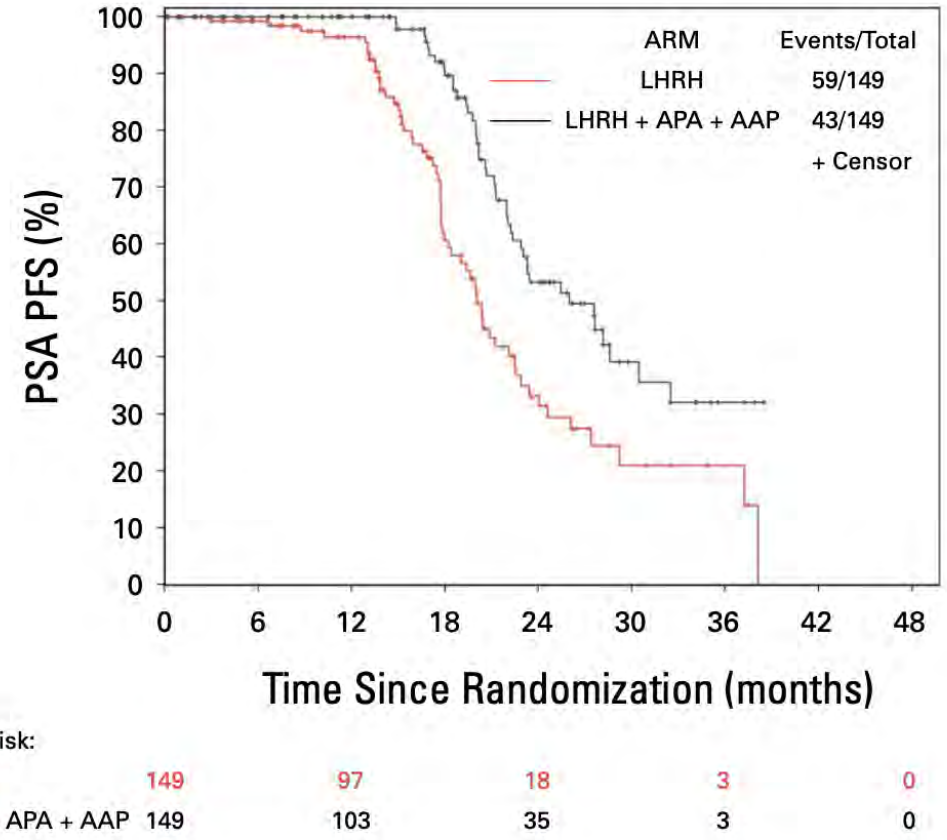


No. at risk:

LHRH	143	94	18	2	0
LHRH + APA	145	101	32	3	0

HR 0.52 [95% CI, 0.35 to 0.77]; P=0.00047

ADT vs ADT + apalutamide +abiraterone



No. at risk:

LHRH	149	97	18	3	0
LHRH + APA + AAP	149	103	35	3	0

HR 0.48 [95% CI, 0.32 to 0.71]; P=0.0008

Aggarwal et al (2024) *J Clin Oncol* 42:1114-1123

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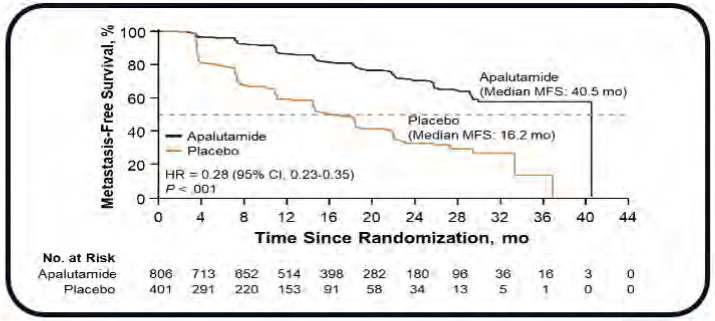
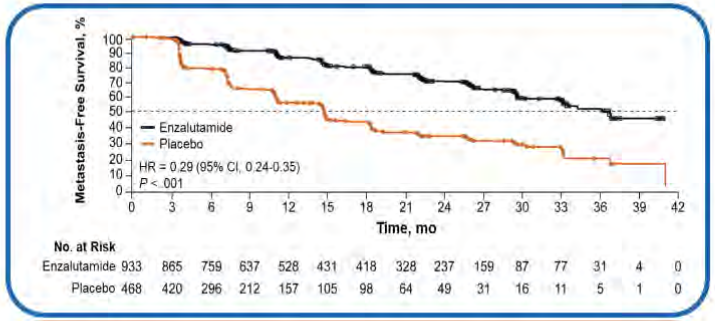
Role of AR Pathway Inhibitors in Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC)

SPARTAN[1]
Apalutamide



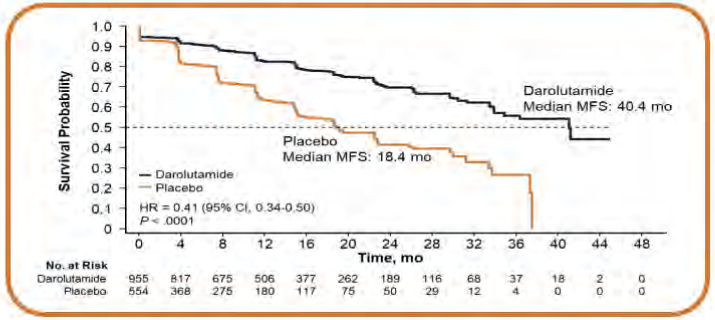
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

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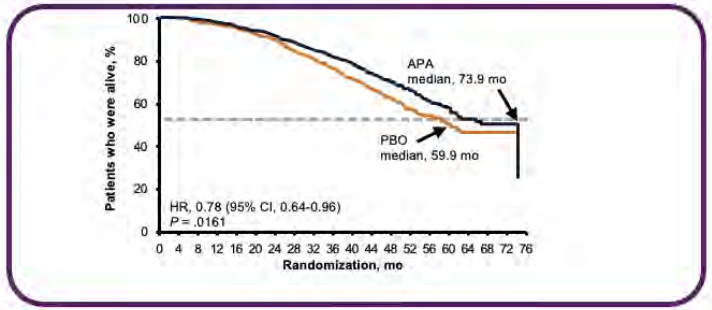
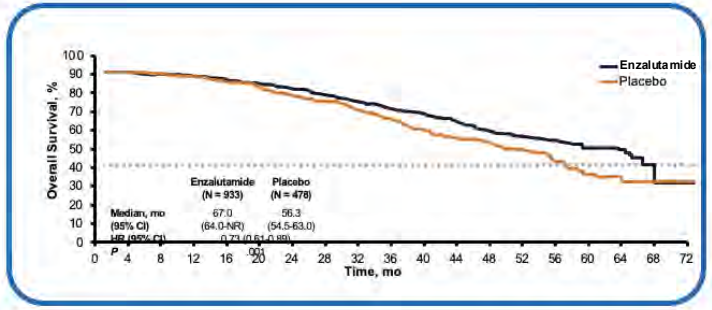
Role of AR Pathway Inhibitors in Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC)

SPARTAN[1]
Apalutamide



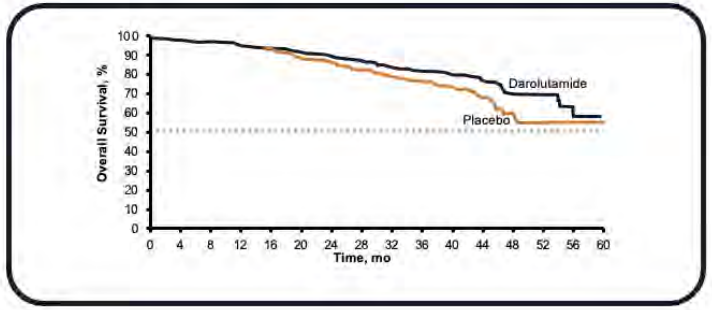
- 22% reduction in risk of death
- Median follow-up of 52.0 mo
- Median OS was significantly longer for apalutamide vs placebo
  - 73.9 mo vs 59.9 mo
  - **HR = 0.78 (95% CI 0.64-0.96); *P* = .016**

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*. 2020;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.

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

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

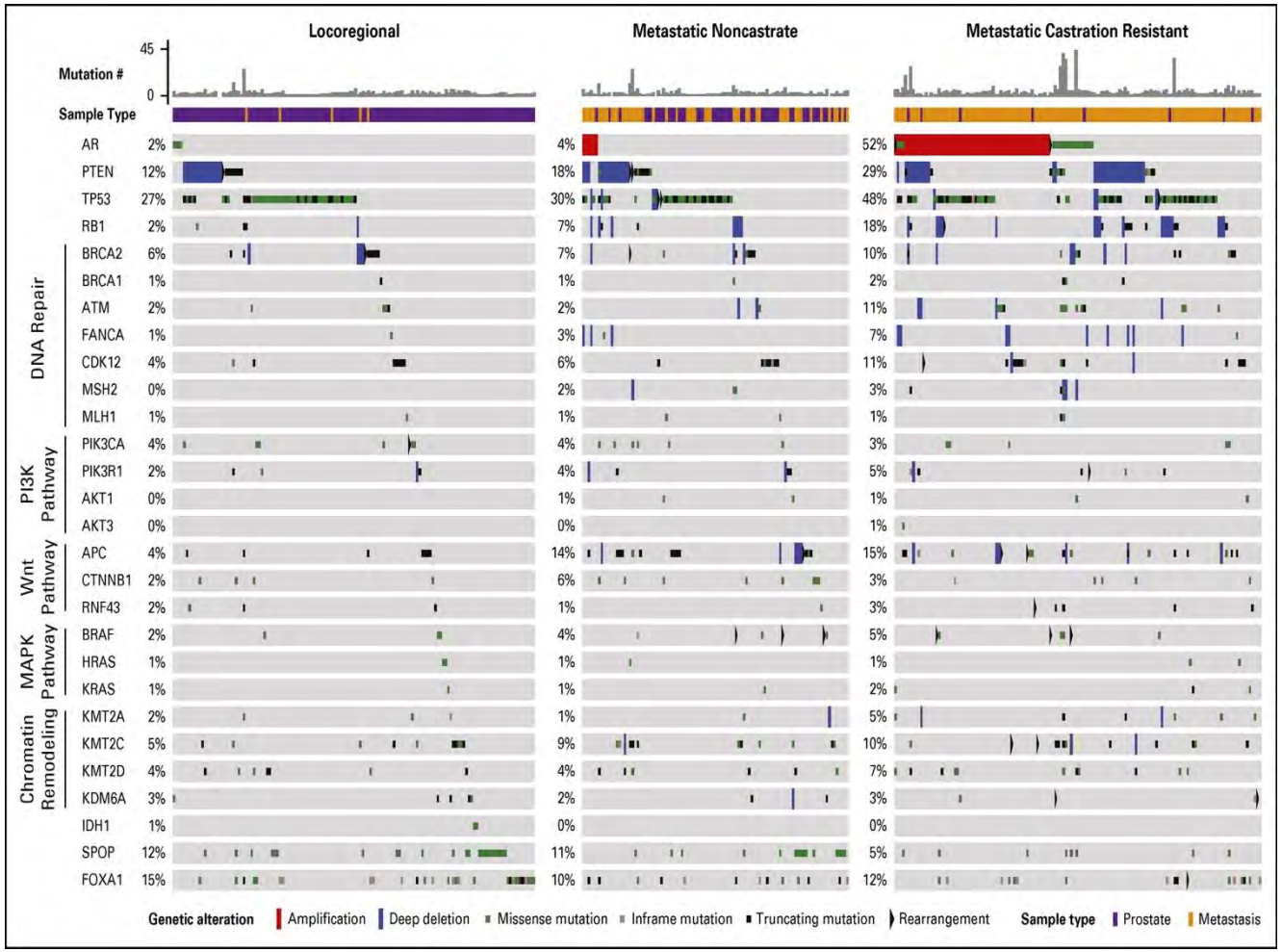
CRPC: Module 2
Other Available and Emerging Therapeutic Approaches

Sandy Srinivas, MD

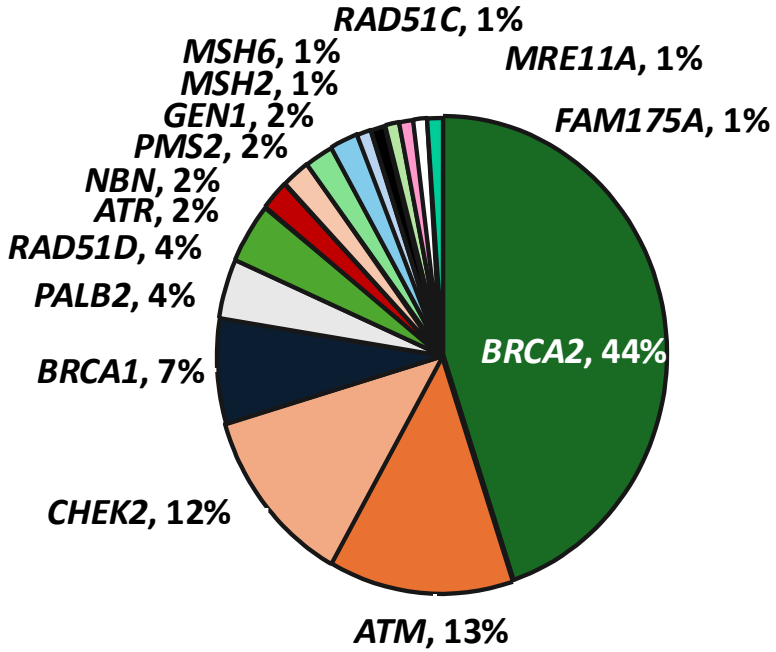
Mutational Landscape by Disease State

Genomic progression from localized disease to mCRPC

- *BRCA1*: 1% to 2%
- *BRCA2*: 6% to 10%
- *ATM*: 2% to 11%
- *FANCA*: 1% to 7%



Distribution of Presumed Pathogenic Germline Mutations



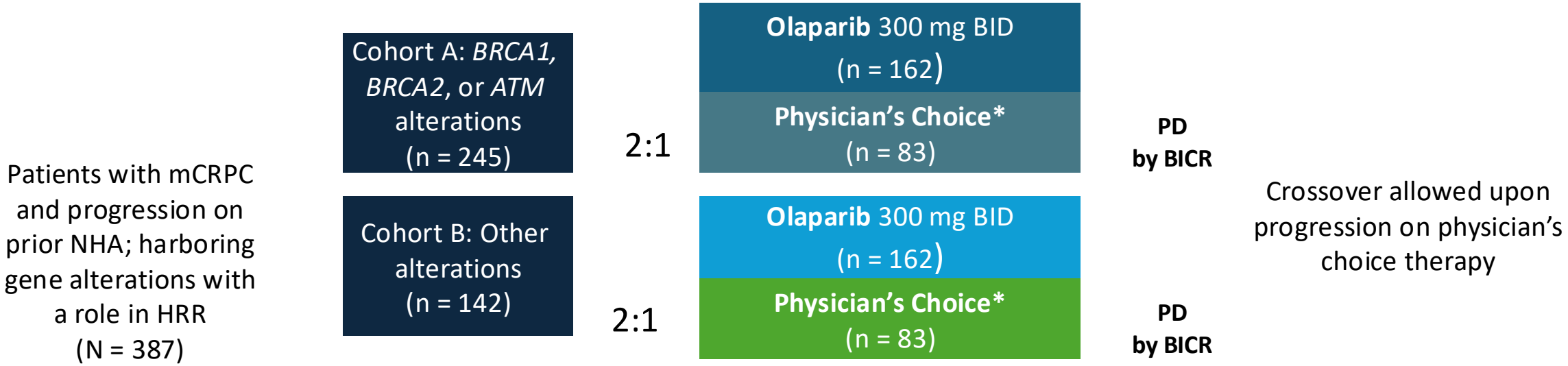
Actionable Mutations

Overall : 23%

Abida. JCO Precision Oncol. 2017;PO.17.00029 Pritchard. NEJM. 2016;375:443

Phase III PROfound: Olaparib vs Physician's Choice in Progressing Metastatic CRPC

Stratified by previous taxane (yes vs no) and measurable disease (yes vs no)



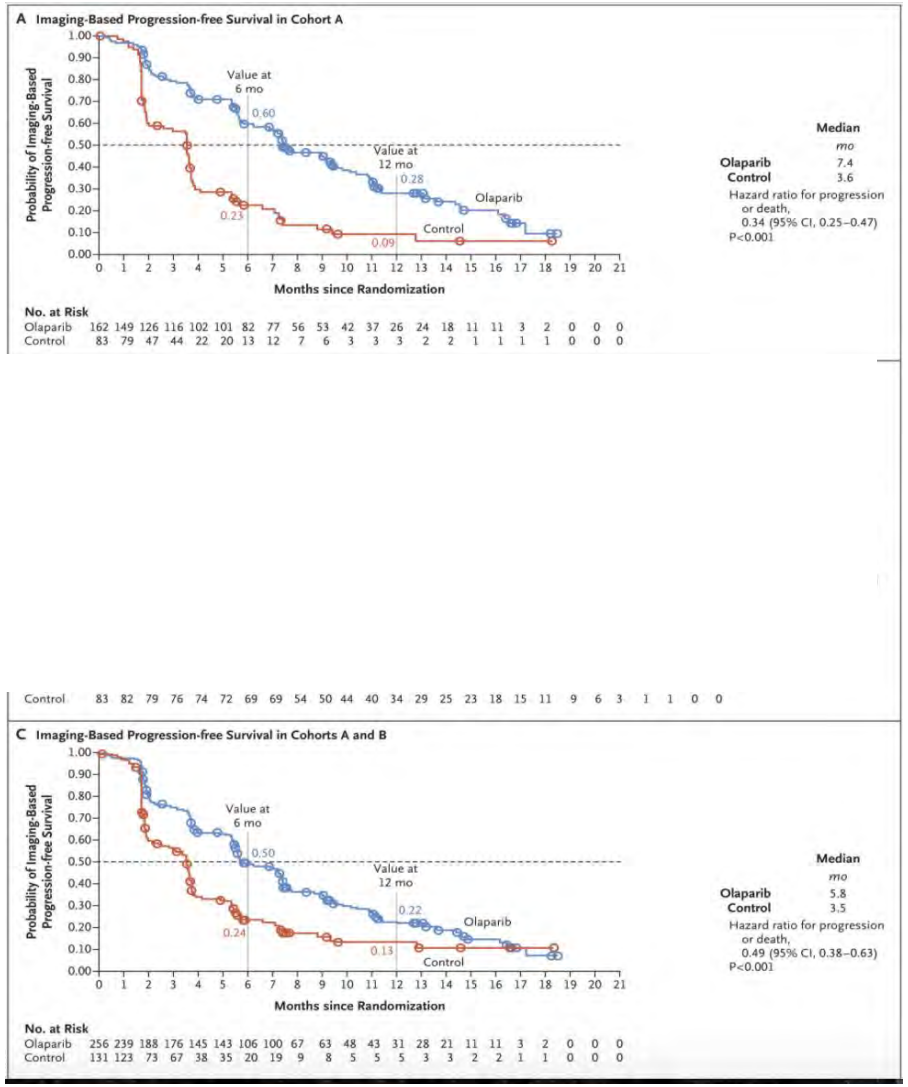
*Enzalutamide 160 mg QD or abiraterone acetate 100 mg QD plus prednisone 5 mg BID.

†***BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L***.

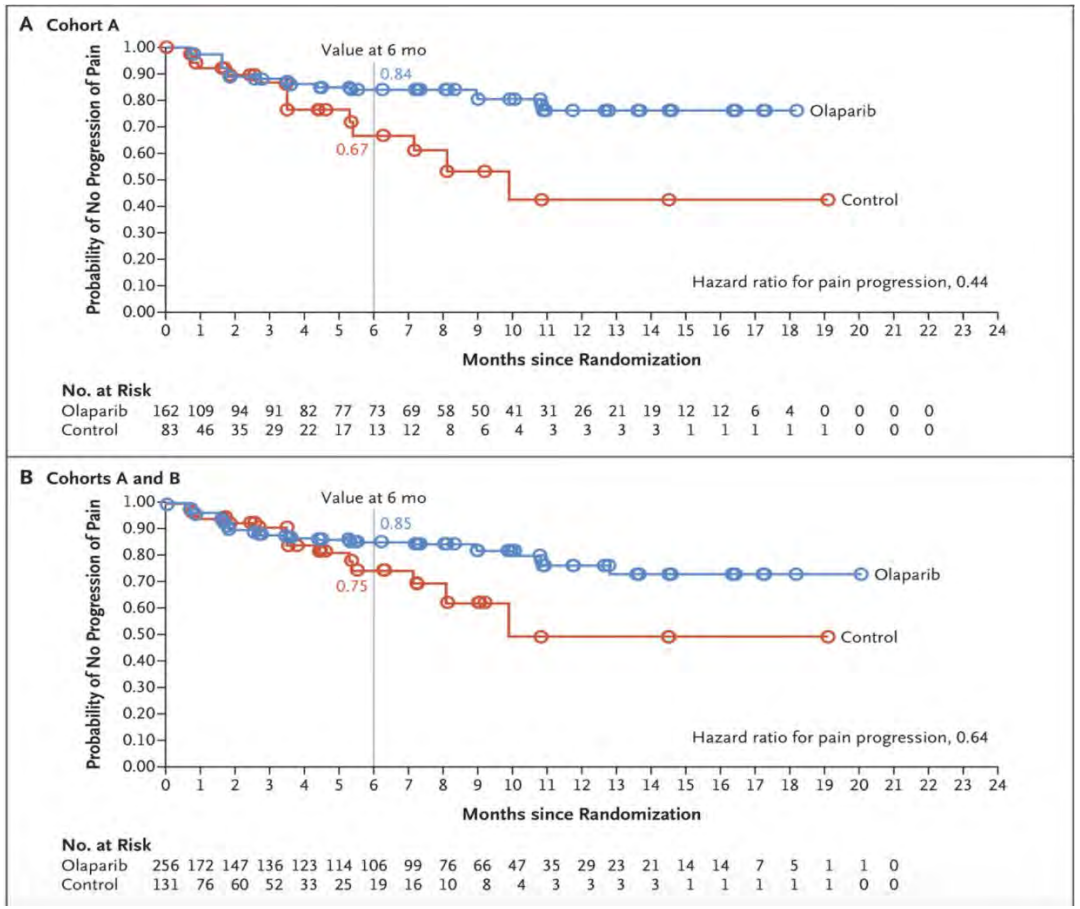
- Primary endpoint: radiographic PFS in Cohort A using RECIST 1.1 and PCWG3 by BICR
- Secondary endpoints: radiographic PFS in both cohorts, confirmed radiographic ORR in Cohort A, time to pain progression in Cohort A, OS in Cohort A

Hussain. NEJM 2020; de Bono. NEJM. 2020;382:2091.

Primary Endpoint: rPFS

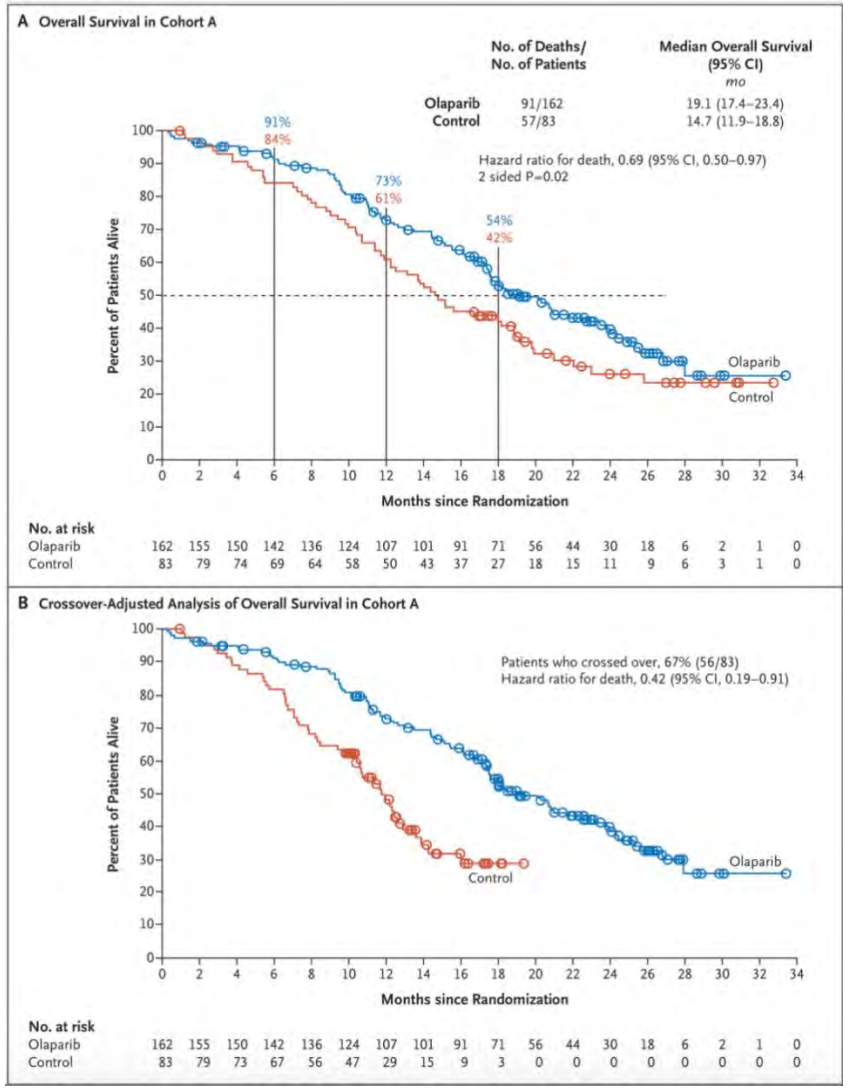


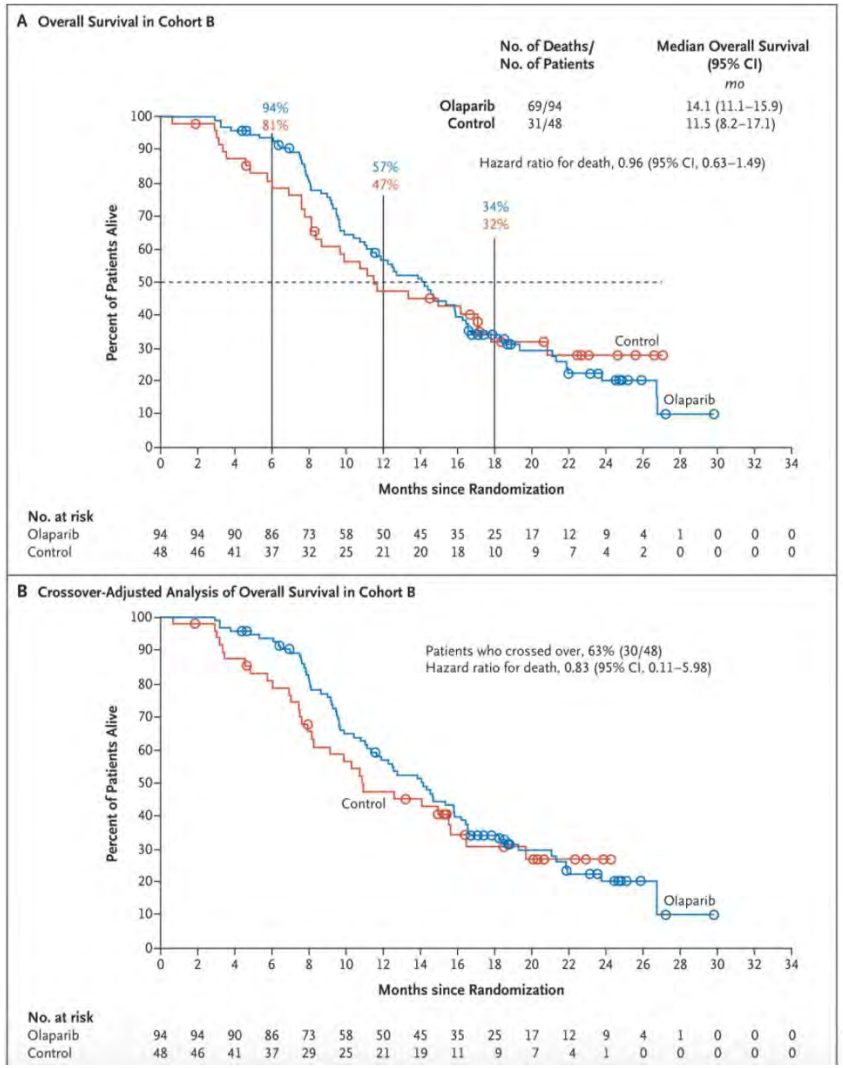
Sec EP: Pain Progression

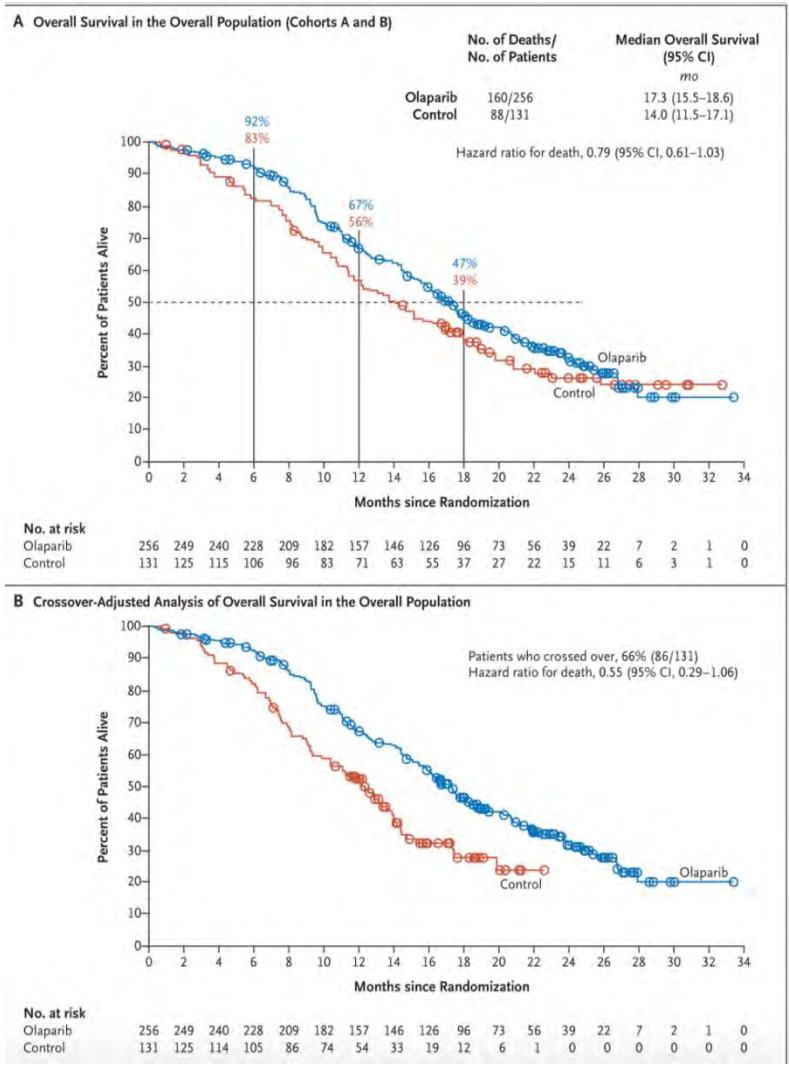


DeBono NEJM 2020

PROfound OS: Cohorts A/B/Overall







FDA approval May 19, 2020 for patients with HRR mutations who have progressed after abiraterone/enzalutamide

TRITON3: **Rucaparib vs Physician's Choice in Progressing mCRPC With *BRCA1/2* or *ATM* Alterations**

- Randomized, ongoing, multicenter, open-label phase III study

*Stratification by ECOG PS (0 or 1), hepatic metastases (yes or no), and genetic alteration (*BRCA1, BRCA2, *or* ATM*)*

Patients with mCRPC; deleterious somatic or germline alteration in ***BRCA1/2* or *ATM***; progression on ARPI in any setting; ECOG PS 0/1; no prior PARPi or CT for CRPC
(N = 405)

2:1

Rucaparib 600 mg BID
x 28-day cycles
(n = 270)

Physician's Choice*
(n = 135)

Until radiographic progression or discontinuation for other reason

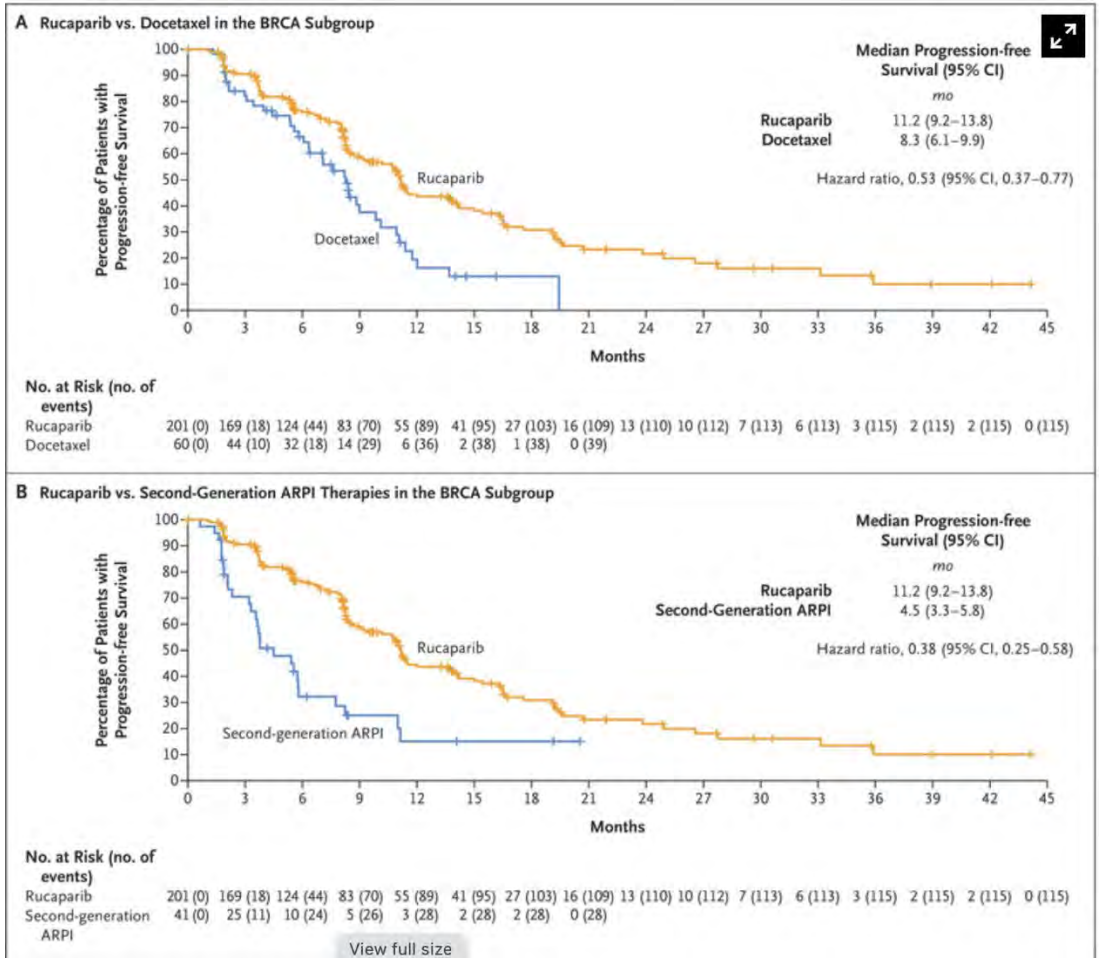
Crossover from CT to rucaparib optional following PD

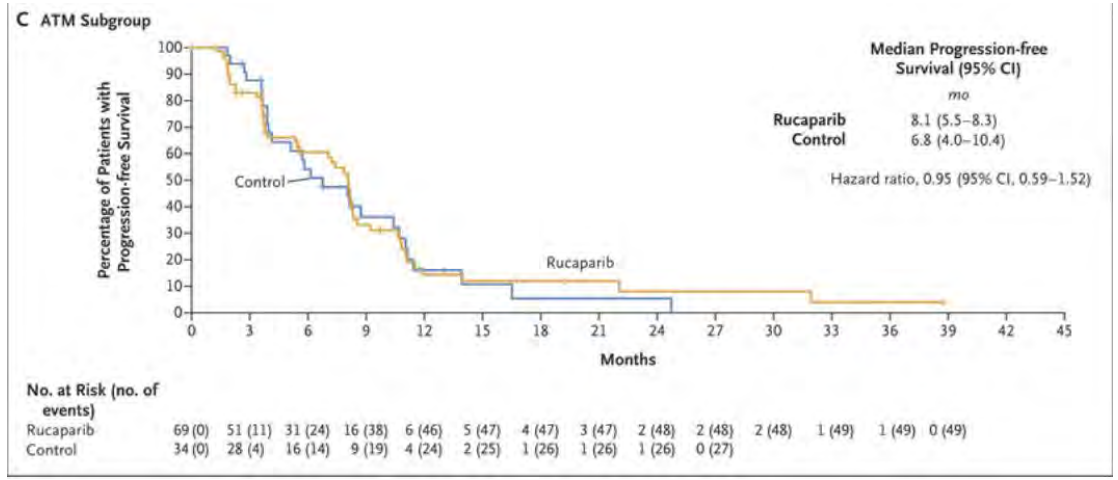
*Docetaxel 75 mg/m^2 in 21-day cycles (max 10 cycles) or abiraterone 1000 mg QD or enzalutamide 160 mg QD. Prednisone coadministered with docetaxel or abiraterone.

- **Primary endpoint:** rPFS by IRR
- **Key secondary endpoints:** OS, ORR by IRR
- **Subgroup analyses:** OS and rPFS for rucaparib vs docetaxel or second-generation ARPI

Bryce. ASCO GU 2023. Abstr 18. Fizazi. NEJM. 2023;388:719.

TRITON3 : Results





May 15 2020 approval in mCRPC post NHT/docetaxel with BRCA mutation

Fizazi NEJM 2023

PARP Combinations

	PROpel	MAGNITUDE	TALAPRO-2
Genes	ATM, BRCA, BARD1, BRP1,CDK12,CHK1/2; FANCL, PALB2, RAD51B/C,D/54L	ATM, BRCA, BRP1, CDK12, CHK2, FANCA, HDAC2, PALB2	ATM, ATR,BRCA,CK2, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51C
Selection of Patients	UNSELECTED	Biomarker positive Cohort	All Comers/HRR positive patients
HRRm rPFS OS	NR vs NR ; HR-0.5(.3-.7)* NR vs 28.5 HR 0.66(.4-.9)*	16.5 vs 13.7 HR-0.72(.5-.9)* 29.3 vs 32.2 HR-1.01 (.7-1.3)	27.9 vs 16.4 HR-0.46(.30.7)* NR vs 33.7 HR-0.69 (.4-1.0)
Non HRRm rPFS OS	24.1 vs 19 HR-0.76 (.6-.9)* 42.1 vs 38.9 HR 0.89(.7-1.1)	NR vs NR HR-1.09 (.7-1.5)	NR vs 22.5 HR-0.7 (.5-.8)* NR vs 38.7 HR-0.9 (.7-1.1)
BRCA rPFS OS	NR vs 8.4 HR-0.23 (.1-.4) * NR vs 23 HR-0.29 (.1-.5)*	16.6 vs 10.9 HR -0.53 (.3-.7)* 30.4 vs 28.6 HR-0.79 (.5-1.1)	NR vs NR HR- 0.23 (.1-.5)* NR vs NR HR 0.61 (.3-1.2)
Non BRCA rPFS OS	24.1 vs 19 HR-0.76 (.6-.9)* 39.6 vs 38 HR-0.91 (.7-1.1)		NR vs NR HR-0.66 (.3-1.1)
Prior ARPI	0.15%	3	8
Prior Docetaxel	24	19	29
FDA label	BRCA mutated CRPC	BRCA mutated CRPC	HRR mutated CRPC

Talazoparib in Combination with Enzalutamide Prolongs Overall Survival (OS) in Phase III TALAPRO-2 Trial

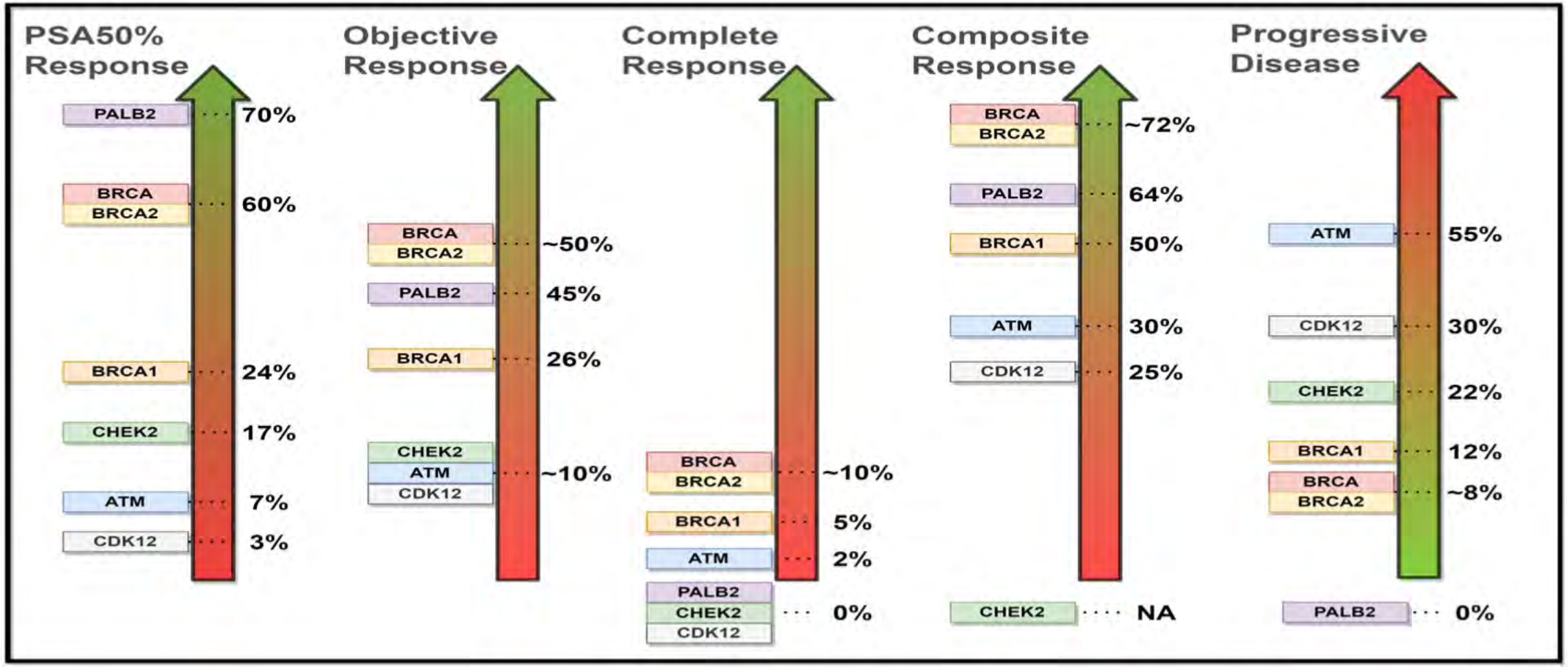
Press Release: October 10, 2024

"The manufacturer announced positive topline results from the final prespecified OS analysis of the TALAPRO-2 study of talazoparib, an oral poly ADP-ribose polymerase inhibitor, in combination with enzalutamide, an androgen receptor pathway inhibitor, for patients with metastatic castration-resistant prostate cancer (mCRPC). Results showed a statistically significant and clinically meaningful improvement in the final OS in all-comers (cohort 1) as well as in those patients with mCRPC with a homologous recombination repair gene mutation (cohort 2), compared to enzalutamide alone.

At the time of the final analysis, the clinically meaningful improvement in radiographic progression-free survival was maintained in both cohorts from the prior primary analysis previously reported and published in *The Lancet*. In addition, the safety profile of talazoparib in combination with enzalutamide was generally consistent with the known safety profile of each medicine. Detailed results from TALAPRO-2 will be submitted for presentation at an upcoming medical congress."

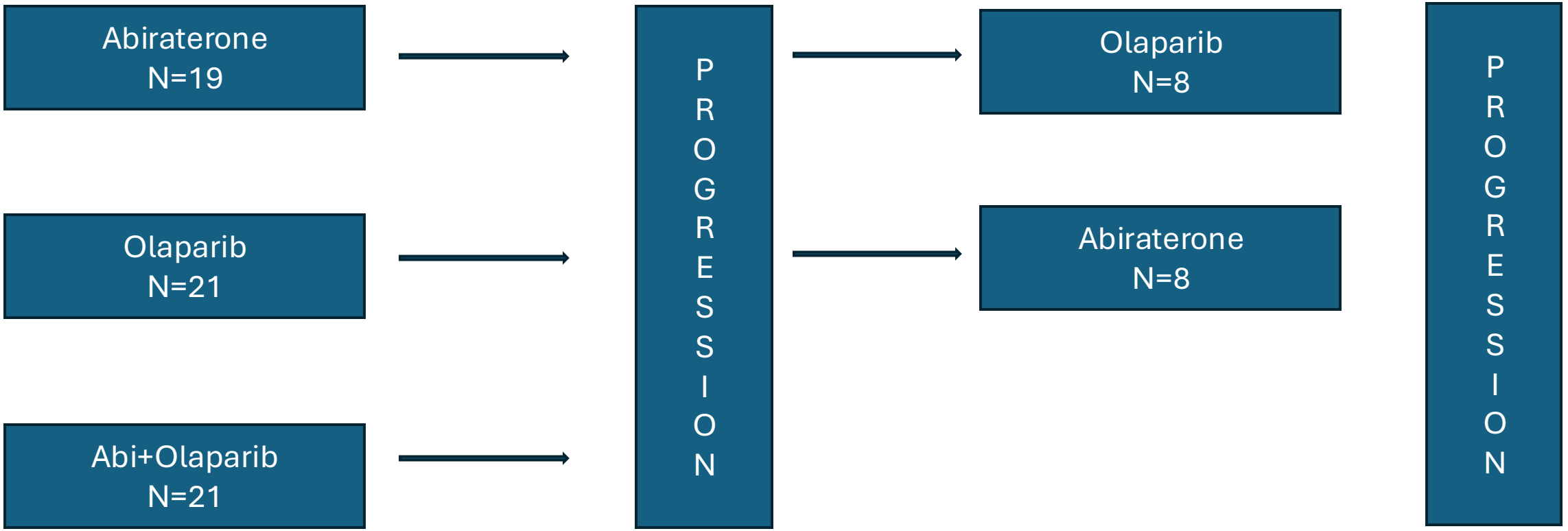
https://www.pfizer.com/news/press-release/press-release-detail/pfizers-talzennar-combination-xtandir-prolongs-overall

Differential Efficacy of PARP Inhibitors in mCRPC With DNA Repair Defects



Naqvi. ASCO GU 2022. Abstr 134.

BRCAAway: DESIGN



Husain GU ASCO 2024

BRCAAway: Results

	Abiraterone	Olaparib	Combination
	Arm I (n = 19)	Arm II (n = 21)	Arm III (n = 21)
Median PFS, months (95% CI)	**8.4 (2.9, 17)**	**14 (8.4, 20)**	**39 (22, NR)**
Objective RR, % (95% CI)	**22** (6.4, 48)	**14** (3, 36)	**33** (15, 57)
PSA RR, % (95% CI)	**61** (36, 83)	**67** (43, 85)	**95** (76, 100)
Undetectable PSA RR, % (95% CI)	**17** (3.6, 41)	**14** (3, 36)	**33** (15, 57)

Crossover

		PFS (mos)	PFS2 (mos)	ORR	PSA50
Abi-Olaparib	8/19	8.3	16	38	50
Olaparib-Abi	8/21	7.2	21	25	63

Husain GU ASCO 2024

Significant Cross Resistance with NHT: Results of the control arm

Contemporary trials looking at alternate NHT in the control arm

	PSA50 (%)	rPFS (mos)	OS	Ref
PROFOUND	8	3.5	19.1 HR-0.69	DeBono NEJM 2020
CONTACT-02	12	4.2	-	Agarwal GUASCO 2023
IMbassador250	3	4.1	-	Powles Nat Med 2022
PSMAfore	20	5.5	-	Sartor ESMO 2023

Low response of monoRx ARSI
Does a combo with PARPi add to just more toxicity?

NCCN Guidelines 2024

No prior docetaxel/no prior novel hormone therapy[qqq]	Progression on prior novel hormone therapy/no prior docetaxel[qqq]
• Preferred regimens ▸ Abiraterone[y,rrr] (category 1[sss]) ▸ Docetaxel[lll] (category 1) ▸ Enzalutamide[y] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 1) ▸ Olaparib/abiraterone[y,lll,rrr,uuu] for *BRCA* mutation (category 1) ▸ Pembrolizumab for MSI-high (MSI-H)/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] (category 1) ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[y]	• Preferred regimens ▸ Docetaxel (category 1)[lll] ▸ Olaparib for *BRCA* mutation[yyy] (category 1) ▸ Rucaparib for *BRCA* mutation[zzz] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 2B) ▸ Olaparib for HRR mutation other than *BRCA1/2*[yyy] ▸ Pembrolizumab for MSI-H/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 2B) • Other recommended regimens ▸ Other secondary hormone therapy[aaaa]
Progression on prior docetaxel/no prior novel hormone therapy[qqq]	**Progression on prior docetaxel and a novel hormone therapy[qqq]**
• Preferred regimens ▸ Abiraterone[y,rrr] (category 1) ▸ Cabazitaxel[lll] ▸ Enzalutamide[y] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[lll] ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation ▸ Olaparib/abiraterone[y,lll,rrr,uuu] for *BRCA* mutation ▸ Pembrolizumab for MSI-H/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] • Other recommended regimens ▸ Other secondary hormone therapy[y]	• Preferred regimens ▸ Cabazitaxel[lll] (category 1) ▸ Docetaxel rechallenge[lll] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[bbbb] (category 1) ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[lll] ▸ Olaparib for HRR mutation[yyy] (category 1) ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[lll] ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Rucaparib for *BRCA* mutation[zzz] • Other recommended regimens ▸ Other secondary hormone therapy[aaaa]

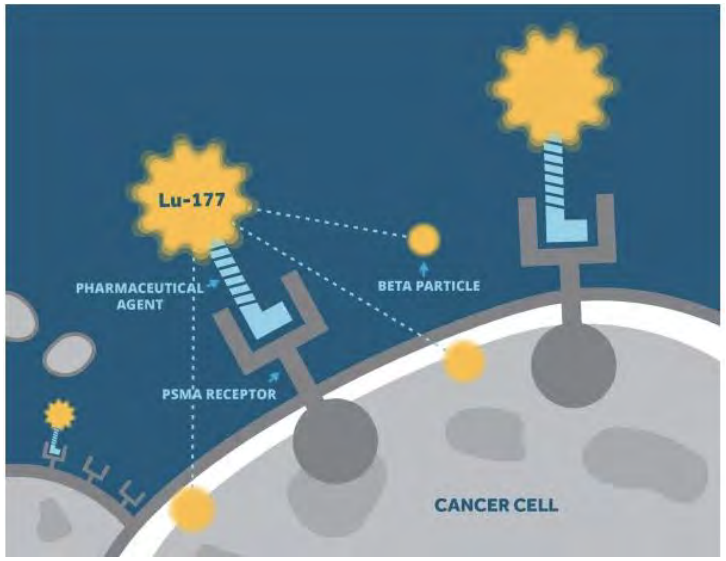
	NHT+ Doce-	NHT+ Doce+
Olaparib-BRCA	1	
Olaparib-HRR	2A	1
Rucaparib	1	2A

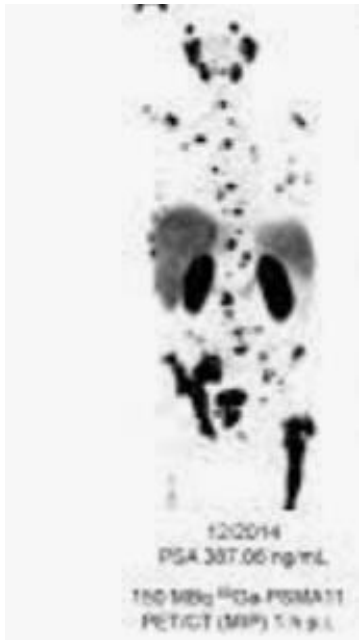
	NHT-- Doc--	NHT— Doc-+	NHT-+ Doc +
Nira/Abi-BRCA	1	2A	2B
Ola/Abi-BRCA	1	2A	
Tala/Enza-HRR	1	2A	2B

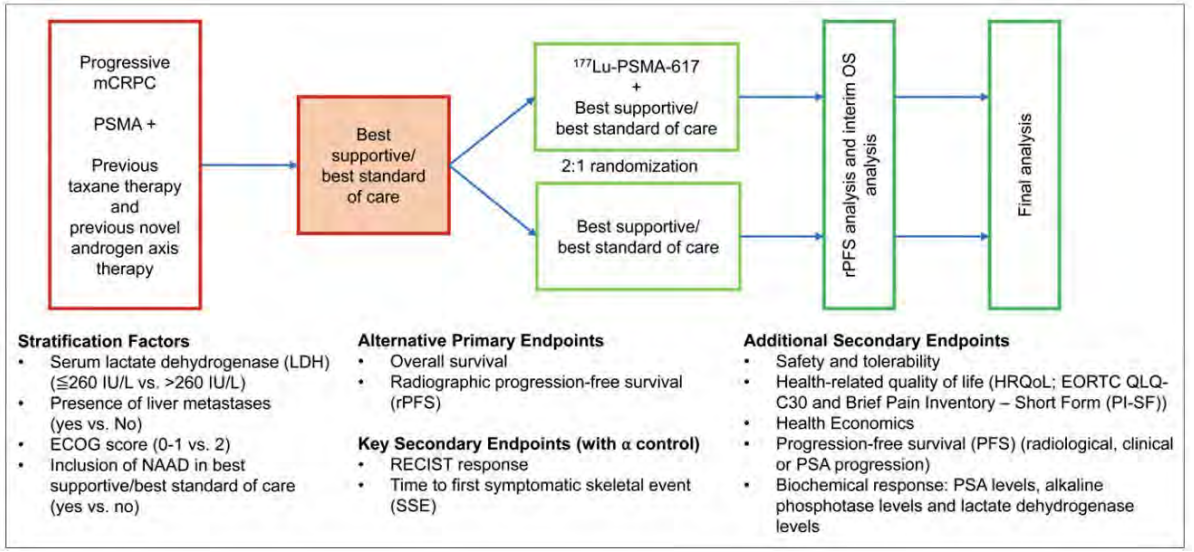
Ongoing trials in mHSPC

Trial	Estimated #	Control arm	Experimental arm	Estimated completion date
AMPLITUDE NCT04497844	696	ADT/Abi/pred	ADT/Abi/pred/ Niraparib	11/2024
TALAPRO-3 NCT04821622	599	ADT/enza	ADT/enza/ Talazoparib	9/2025

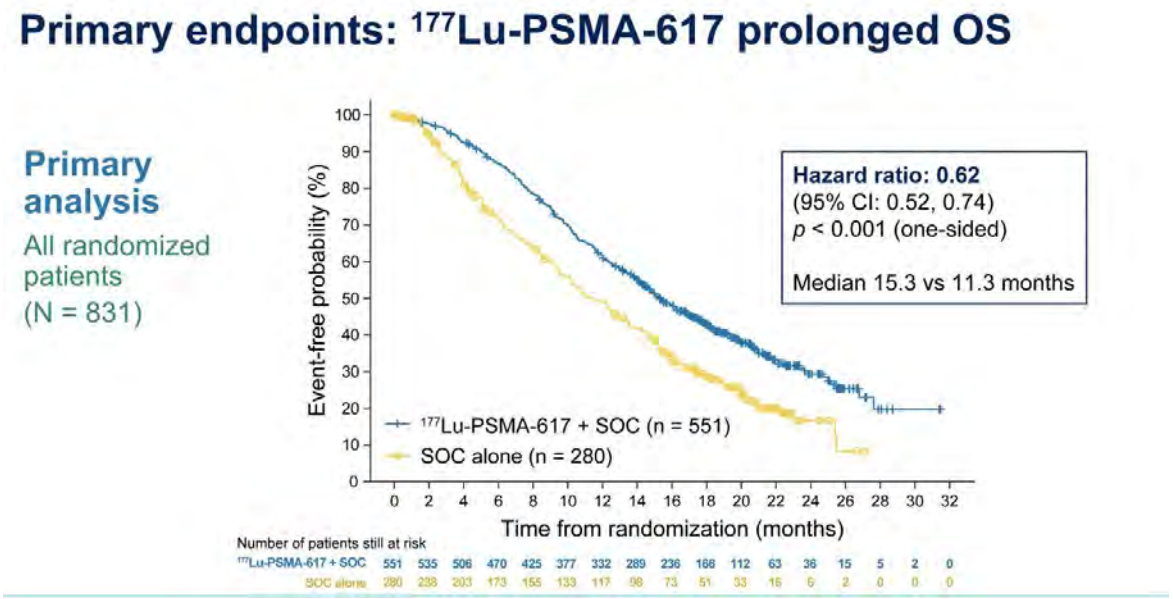
VISION: Phase 3 randomized study Lu177

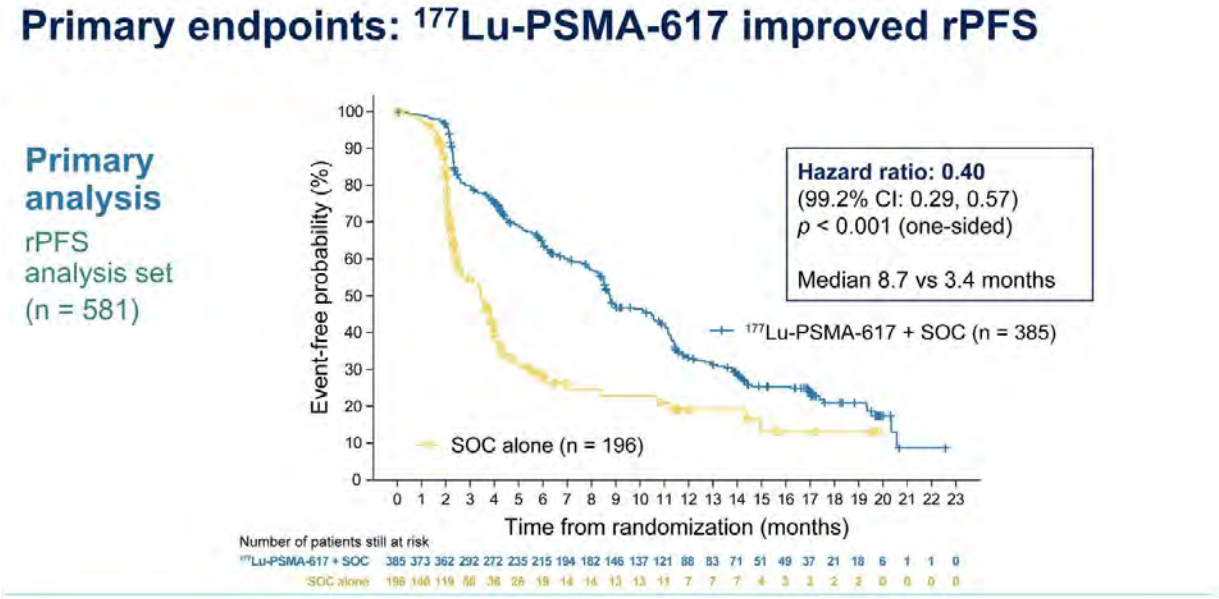






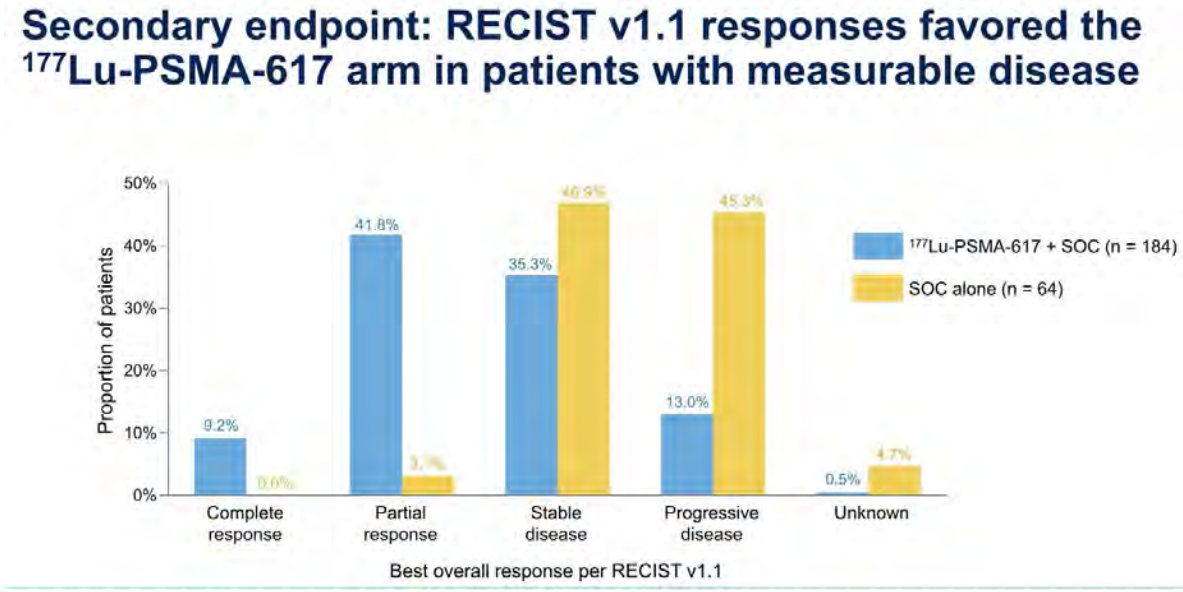
Primary Endpoints: Improved Overall survival/rPFS



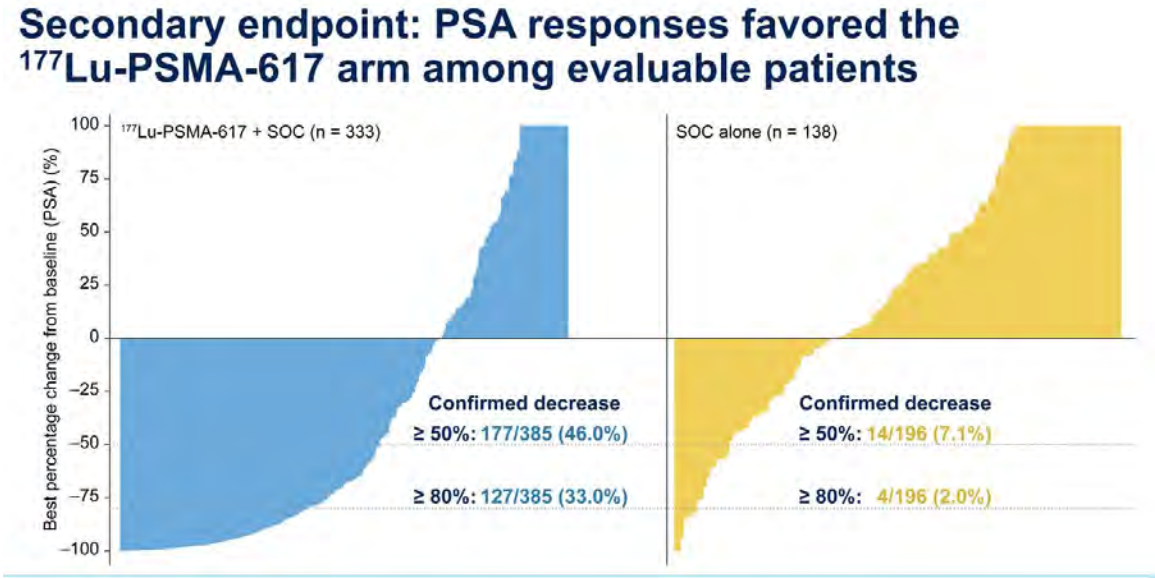


Sartor *N Engl J Med* 2021; Morris ASCO 2021

Secondary Endpoints: Measurable Disease and PSA responses

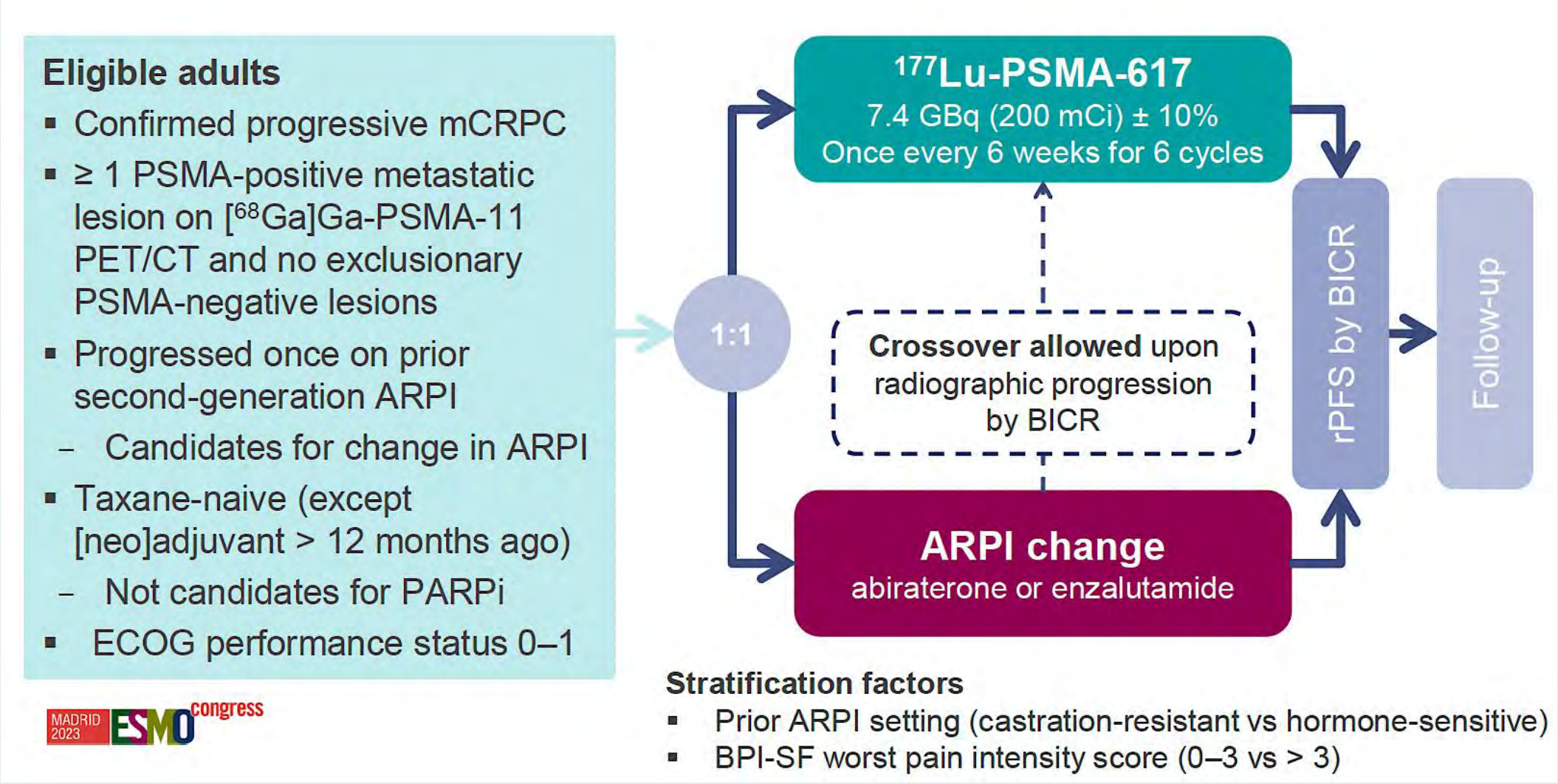


FDA approved in heavily pre-treated patients post NHT and post taxanes



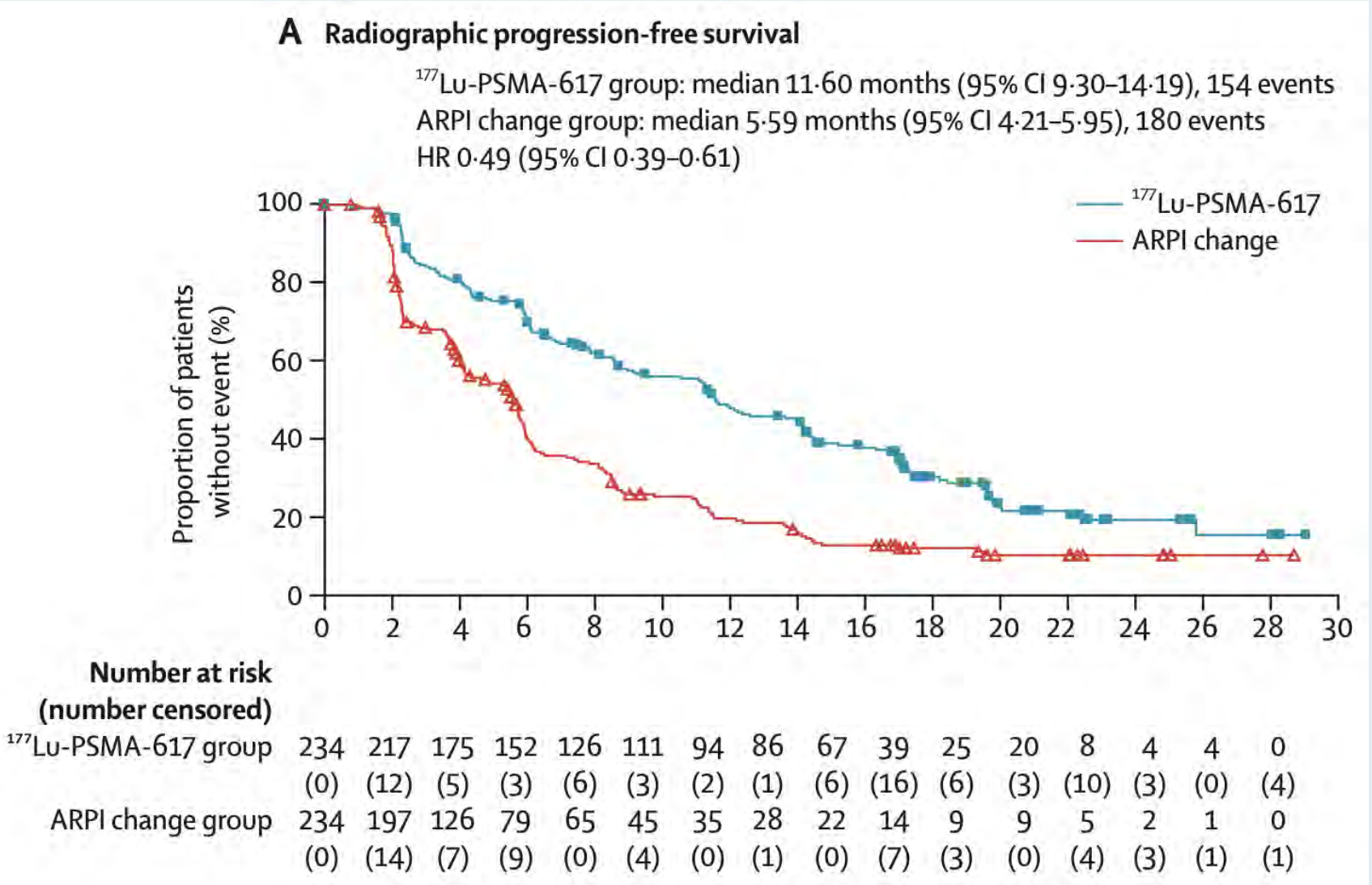
Morris M et al. ASCO 2021

PSMAfore: A Phase III Study of Lutetium Lu 177 Vipivotide Tetraxetan versus a Change of Androgen Receptor Pathway Inhibitor (ARPI) for Patients with Taxane-Naïve Progressive mCRPC



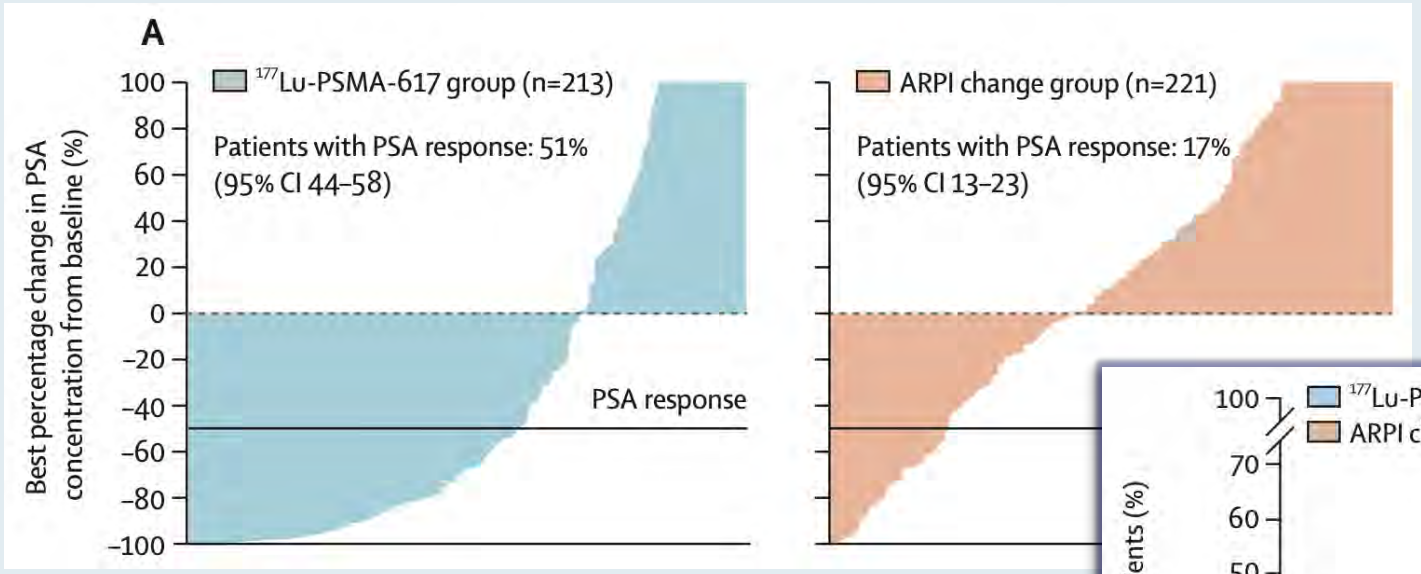
Morris MJ et al. *Lancet* 2024;404(10459):1227-39. Sartor O et al. ESMO 2023;Abstract LBA13.

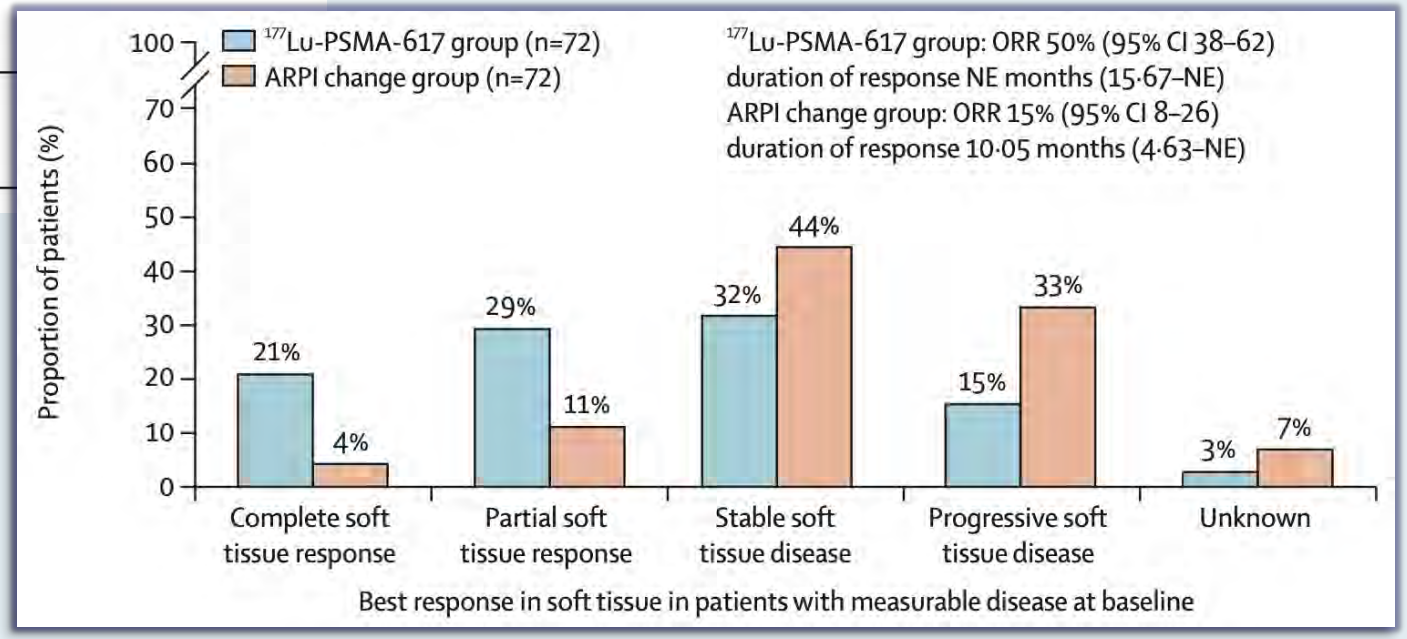
PSMAfore: A Phase III Study of Lutetium Lu 177 Vipivotide Tetraxetan versus a Change of ARPI for Patients with Taxane-Naïve Progressive mCRPC – Progression-Free Survival



Morris MJ et al. *Lancet* 2024;404(10459):1227-39.

Lutetium Lu 177 Vipivotide Tetraxetan versus a Change of ARPI: Changes in PSA and Responses in Soft Tissue in PSMAfore





Morris MJ et al. *Lancet* 2024;404(10459):1227-39.

Lutetium Lu 177 Vipivotide Tetraxetan versus a Change of ARPI: Safety Profile in PSMAfore

AEs, n (%)	All grades		Grades 3–5	
	^{177}Lu-PSMA-617 (n = 227)	ARPI change (n = 232)	^{177}Lu-PSMA-617 (n = 227)	ARPI change (n = 232)
Dry mouth	130 (57.3)	5 (2.2)	3 (1.3)	0
Asthenia	72 (31.7)	67 (28.9)	1 (0.4)	8 (3.4)
Nausea	71 (31.3)	28 (12.1)	0	1 (0.4)
Anaemia	55 (24.2)	39 (16.8)	14 (6.2)	14 (6.0)
Fatigue	52 (22.9)	59 (25.4)	0	4 (1.7)
Constipation	50 (22.0)	31 (13.4)	1 (0.4)	0
Decreased appetite	48 (21.1)	42 (18.1)	0	1 (0.4)
Arthralgia	43 (18.9)	48 (20.7)	0	1 (0.4)
COVID-19	37 (16.3)	26 (11.2)	1 (0.4)	1 (0.4)
Diarrhoea	37 (16.3)	20 (8.6)	0	1 (0.4)
Back pain	28 (12.3)	38 (16.4)	2 (0.9)	5 (2.2)
Vomiting	26 (11.5)	11 (4.7)	0	0
Peripheral oedema	19 (8.4)	26 (11.2)	0	0
Weight loss	15 (6.6)	28 (12.1)	2 (0.9)	5 (2.2)

AEs = adverse events

Morris MJ et al. *Lancet* 2024;404(10459):1227-39. Sartor O et al. ESMO 2023;Abstract LBA13.

SPLASH: PSMAfore

SPLASH (I&T) – comparable with PSMAfore (617)

Screening

- Progressive mCRPC, Progressed on previous treatment with one ARPI
- **PSMA-avid PET – no FDG PET**
- ECOG 0 to 1, Taxane for HSPC allowed (>1 year prior to consent)

Randomization

2:1

- ^{177}Lu-PNT2002 6.8 GBq (±10%) every 8 weeks up to 4 — 276
- Alternate ARPI enzalutamide or abiraterone — 136

1:1

- ^{177}Lu-PSMA-617 7.4 GBq (±10%) every 6 weeks up to 6 — 234
- ARPI Change enzalutamide or abiraterone — 234

Crossover allowed

Primary Endpoint: rPFS BICR using RECIST 1.1 for soft tissue lesions and PCWG3 criteria for bone lesions

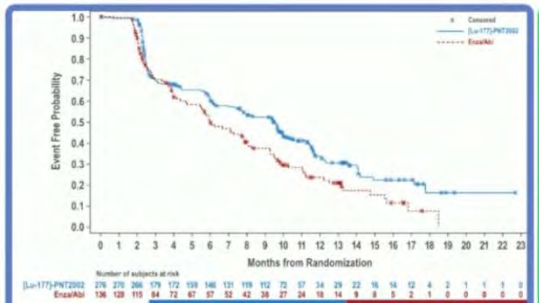
Key Secondary: OS

Further Endpoints: ORR, Time to skeletal event, PSA50 response, bPFS, HRQoL, safety

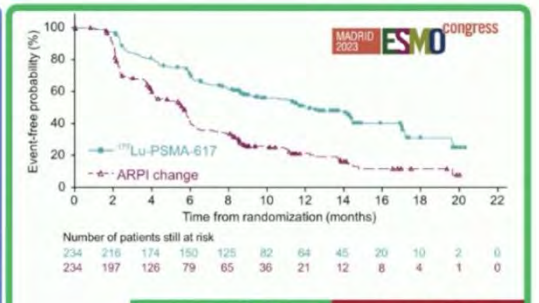
BARCELONA 2024 ESMO congress

MADRID 2023 ESMO congress

SPLASH (I&T) – comparable with PSMAfore (617): rPFS



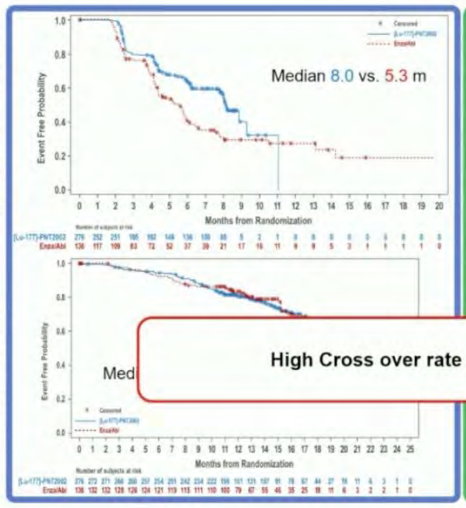
	^{177}Lu-PNT2002 (n = 276)	Alternate ARPI (n = 136)
Events, n	162 (58.7%)	96 (70.6%)
Median rPFS	9.5 months (7.4, 10.0)	6.0 months (4.7, 7.9)
	HR: 0.71 (95% CI: 0.55, 0.92) p = 0.0088	

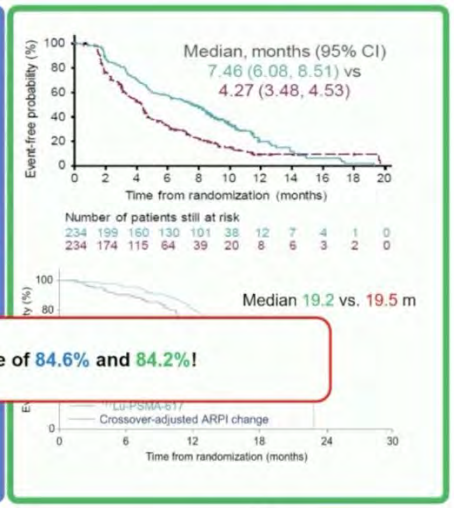


	^{177}Lu-PSMA-617 (n = 234)	Alternate ARPI (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS	12.0 months (9.3, 14.4)	5.59 months (4.17, 5.95)
	HR: 0.43 (95% CI: 0.33, 0.54) p < 0.0001	

FACT-P Score

Interim OS





High Cross over rate of 84.6% and 84.2%!

Sartor ESMO 2024; Sartor ESMO 2023

PEACE-3: Radium 223+Enza vs Enza in mCRPC

EORTC-GUCG 1333 (PEACE-3)

Study population
- Patients with mCRPC and bone metastases
- Asymptomatic or mildly symptomatic*
- WHO PS of 0 or 1
- No prior treatment with enzalutamide or Ra223
- No known visceral metastases
- Ongoing ADT

N=446**

1:1 Randomisation

Ra223
55 kBq/kg iv every 4 weeks for 6 cycles plus
Enzalutamide 160 mg od

Enzalutamide 160 mg od

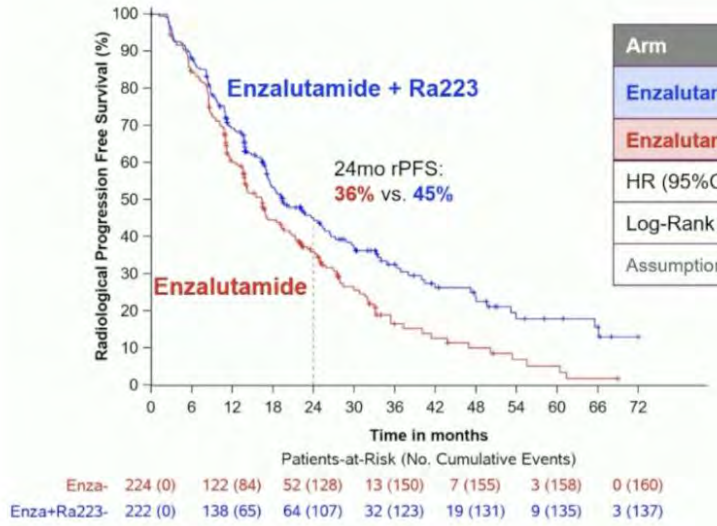
Stratification factors
- Country
- Baseline pain (BPI worst pain 0-1 vs 2-3)
- Prior docetaxel (yes vs no)
- Use of bone protecting agents
- Prior abiraterone (yes vs no)

Primary endpoint
- rPFS

Key secondary endpoints
- Safety
- Overall Survival
- Time to next treatment
- Time to pain progression
- Time to first SSE (symptomatic skeletal event)

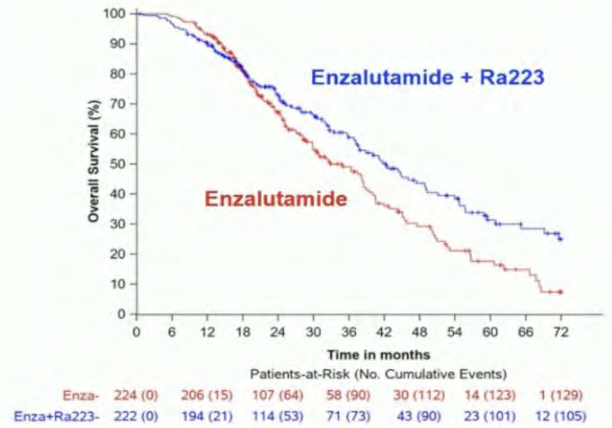
*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

Use of bone protecting agents (BPA) made mandatory (after inclusion of 119 patients)



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95%CI)	**0.69** (0.54-0.87)	
Log-Rank p-value	**0.0009**	
Assumption of proportional hazard achieved		

Overall Survival at interim analysis (80% of OS events)



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo
Enzalutamide	129/224	**35.0** (28.8-38.9) mo
HR (95%CI)	**0.69** (0.52-0.90)	
Log-Rank p-value	**0.0031**	<0.0034

- Pre-set level of significance for interim analysis was ≤ 0.0034
- Due to non-proportional hazards plus lack of unequivocal significance for RMST (restricted mean survival time) sensitivity analysis, study will continue to final OS analysis

Gillessen ESMO 2024

Targeting the AKT pathway

Phase III CAPItello-281: Capivasertib + Abiraterone vs Placebo + Abiraterone in de Novo, PTEN^{def} mHSPC[1]

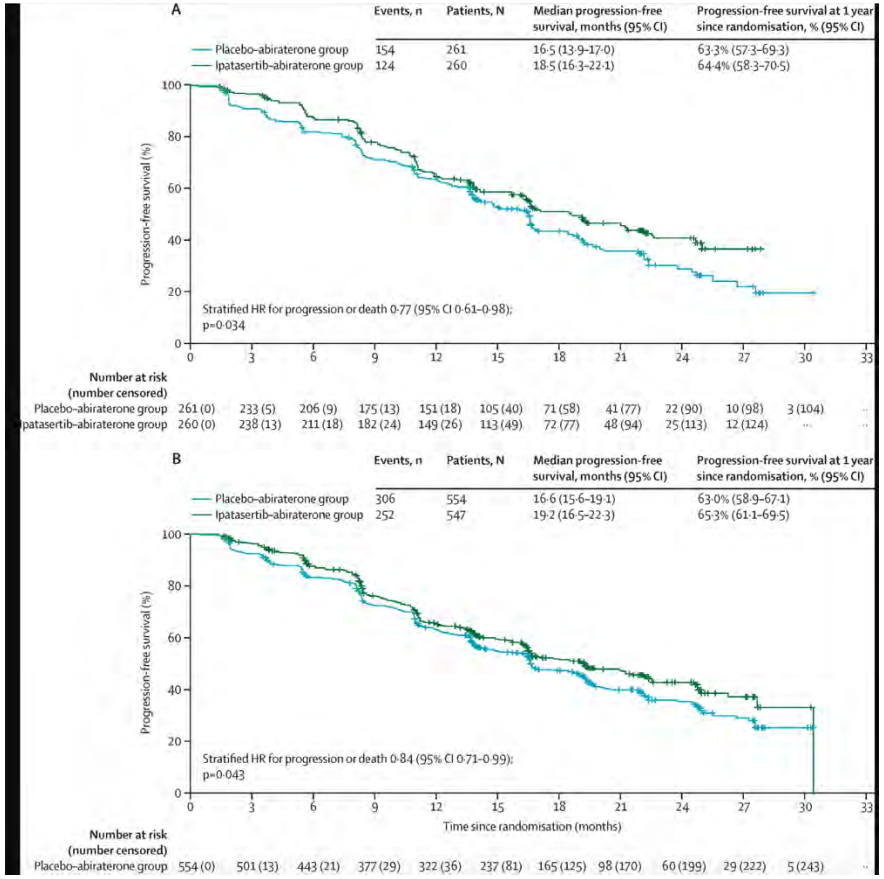
Patients with asymptomatic or mildly symptomatic *de novo* mHSPC with PTEN deficiency; ≥1 bone lesion and/or ≥ soft tissue lesion; previous tx with abiraterone/ steroid allowed for ≤3 mos prior to randomization; ECOG PS 0/1

- **Capivasertib + Abiraterone + Prednisone**
- **Placebo + Abiraterone + Prednisone**

1º EP: rPFS

All patients receive continuous ADT

- IPATential150: ipatasertib+abi vs abiraterone in mCRPC



Sweeney Lancet 2021

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

We are taking a short break!

The program will resume at 9:30 AM ET

Up Next …

Drs Sarah Goldberg and Joshua Sabari discuss the management of lung cancer

Please complete Part 2 of the premeeting survey