Fifth Annual
National General Medical Oncology Summit

Sunday, April 26, 2026

Moderator

Neil Love, MD

Faculty

Neeraj Agarwal, MD, FASCO
Lyudmila Bazhenova, MD
Alan H Bryce, MD
Kristen K Ciombor, MD, MSCI
Courtney D DiNardo, MD, MSCE
Harry Paul Erba, MD, PhD
Jonathan Goldman, MD
Erika Hamilton, MD
Anthony M Hunter, MD
Corey J Langer, MD
Jane Lowe Meisel, MD
Joyce O'Shaughnessy, MD
Zofia Piotrowska, MD, MHS
John Strickler, MD
Seth Wander, MD, PhD
Abdulraheem Yacoub, MD

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Co-Moderators

Susmitha Apuri, MD
Inverness and Lecanto, Florida

Maria Regina Flores, MD
Orlando, Florida

Maen Hussein, MD
The Villages, Florida

Mamta Choksi, MD
Trinity, Florida

Gustavo Adolf Fonseca, MD
Lecanto, Florida

Vikas Malhotra, MD
Spring Hill, Florida

Uday Dandamudi, MD
New Port Richey, Florida

Sunil Gandhi, MD
Lecanto, Florida

Shachar Peles, MD
Lake Worth, Florida

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Maen Hussein, MD

Disclosures for Moderator Neil Love, MD

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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.

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 pre- and postmeeting surveys.

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

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

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from this weekend will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.

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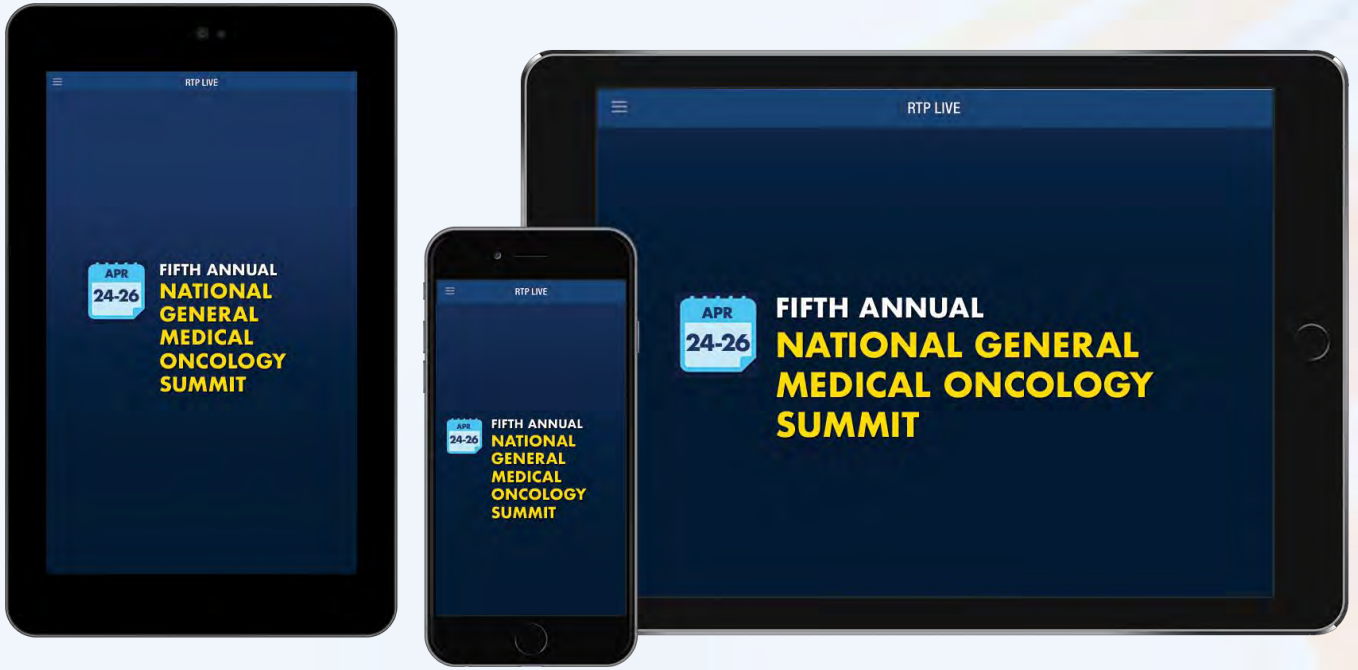

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Module 10: HR-Positive Breast Cancer

Current and Future Management of HR-Positive, HER2-Negative Localized Breast Cancer — Dr Meisel

Optimizing First-Line Therapy for Patients with HR-Positive mBC — Dr Hamilton

Current and Future Role of Oral SERDs for Progressive HR-Positive mBC — Dr Wander

Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr O'Shaughnessy

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QUESTIONS?

Module 10: HR-Positive Breast Cancer

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

CURRENT AND FUTURE MANAGEMENT OF HORMONE RECEPTOR (HR)-POSITIVE, HER2-NEGATIVE EARLY BREAST CANCER (BC)

Fifth Annual National General Medical Oncology Summit
April 28, 2026
Orlando, FL

Jane Lowe Meisel, MD

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

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DISCLOSURES

Advisory Committees	AstraZeneca Pharmaceuticals LP, GE Healthcare, Novartis, Olema Oncology, Pfizer Inc, Sermonix Pharmaceuticals
Consulting Agreements and Contracted Research	AstraZeneca Pharmaceuticals LP, Olema Oncology, Pfizer Inc, Sermonix Pharmaceuticals
Nonrelevant Financial Relationships	ASCO (DSMB, CDK dosing study)

LEARNING OBJECTIVES

- We will review the latest data on adjuvant CDK 4/6 inhibitors and discuss how to apply this data in the clinic
  - MonarchE
  - NATALEE
  - TRADE trial

- We will discuss efficacy and safety outcomes from the phase III lidERA study and how this might ultimately be incorporated into clinical practice

- We will note several ongoing phase III trials of other oral SERDs in the adjuvant setting and possible implications for the future

THE ADVENT OF CDK 4/6 INHIBITORS

- Before 2015, aromatase inhibitors, fulvestrant, tamoxifen, and everolimus were the only endocrine options we had for treating HR+ breast cancer

- After that, patients had to move on to capecitabine and then to IV chemotherapies, making prognosis and quality of life quite limited

- In 2015, palbociclib, the first CDK 4/6 inhibitor, was approved
- In 2018, ribociclib and abemaciclib followed
- These drugs very quickly changed the landscape for patients with metastatic HR+ breast cancer

J Clin Oncol 42, 994-1000(2024). npj Breast Cancer volume 8, Article number: 114 (2022)

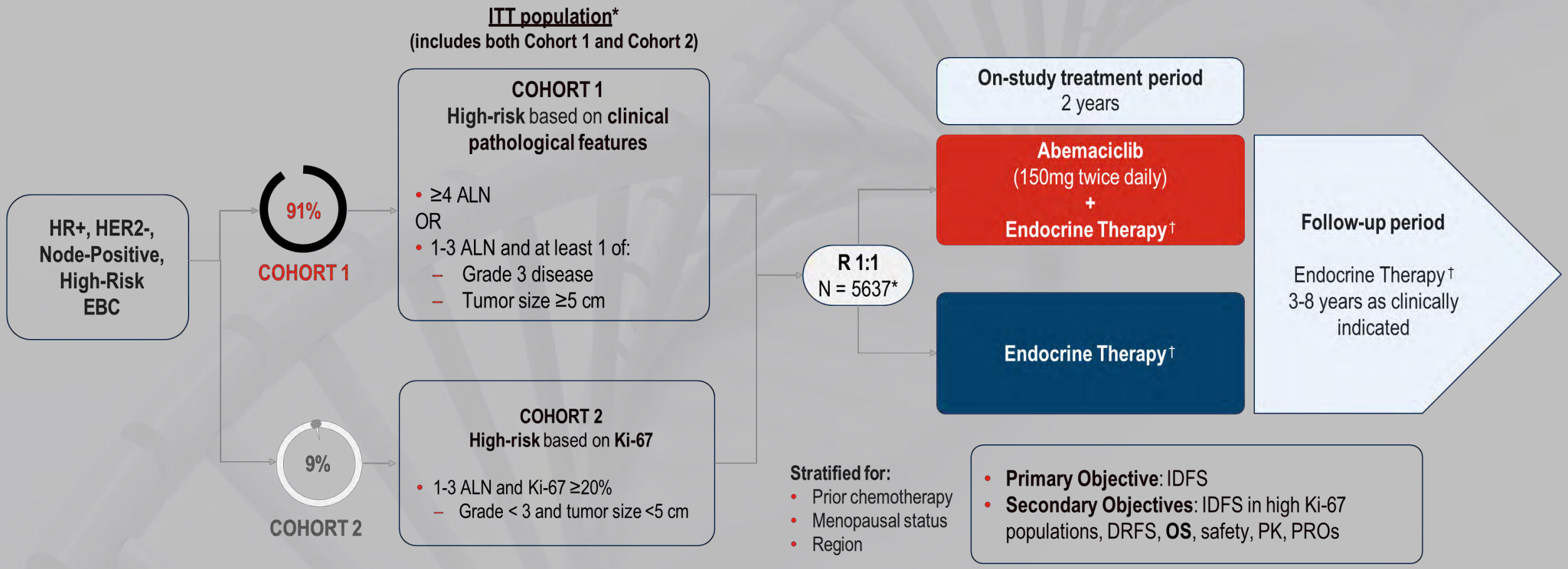
CDK 4/6 INHIBITORS IN HIGH-RISK EARLY STAGE DISEASE

- A decade ago, CDK 4/6 inhibitors revolutionized the care of women with stage IV HR+ breast cancer and became a mainstay of first-line treatment

- As history has shown, the next step for many drugs that do well in the metastatic setting (especially if well tolerated) is to study them upfront

  - We ask: can we cure more high-risk patients with early-stage disease if we use these newer agents in the adjuvant setting?

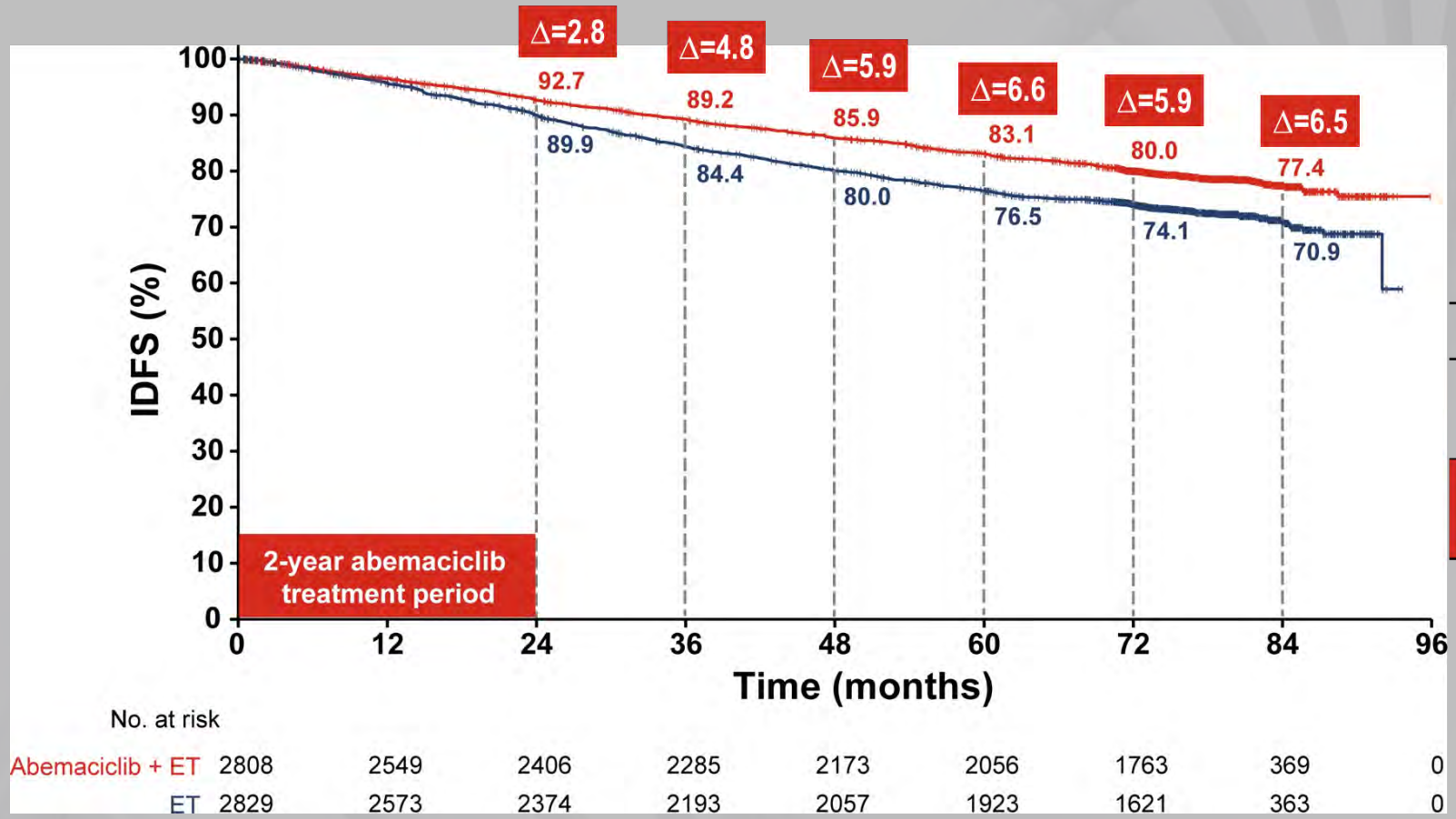
PHASE III MONARCHE TRIAL: DESIGN



Johnston S, et al. ESMO 2025. Abstract LBA13. Johnston S, et al. *Ann Oncol*. Published online October 17, 2025. doi:10.1016/j.annonc.2025.10.005

*Recruitment from July 2017 to August 2019. Patients had to be randomized on trial within 16 months of their definitive surgery and were restricted to taking no more than 3 months of ET alone following completion of all surgery, radiation therapy, and chemotherapy †Endocrine therapy of physician's choice (eg, AI, Tamoxifen, GnRH). Data for the monarchE Cohort 1 population that forms the basis of multiple global approvals is in the supplement.
Johnson S, et al. ESMO 2025. Abstract LBA13. Johnson S, et al. Ann Oncol. Published online October 17, 2025. doi:10.1016/j.annonc.2025.10.005

MONARCHE: IDFS (PRIMARY ENDPOINT)

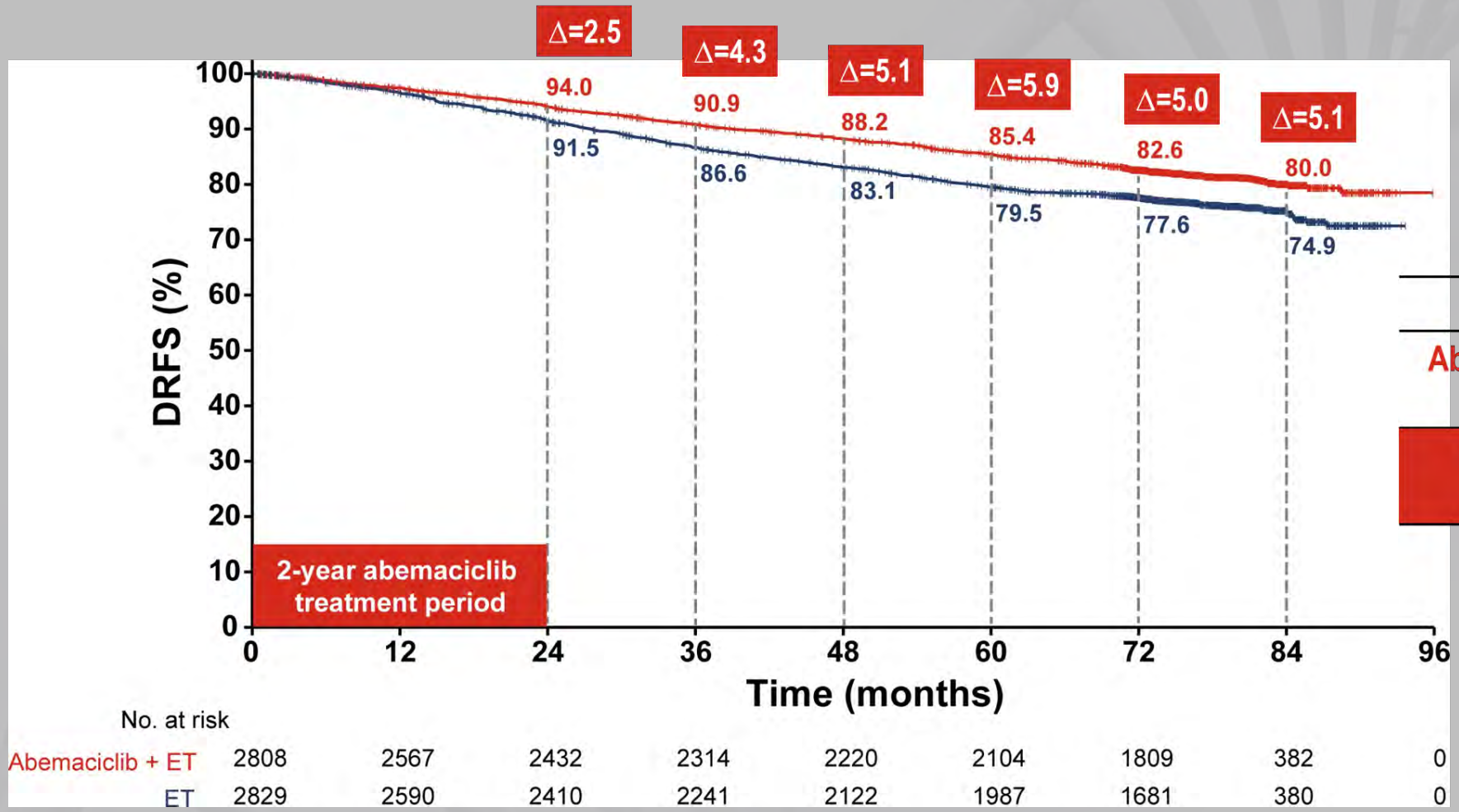


Number of IDFS events	
Abemaciclib + ET	ET
547	722

HR (95% CI): 0.734 (0.657, 0.820)
Nominal *P*<.0001

Johnston S, et al. ESMO 2025. Abstract LBA13. Johnston S, et al. *Ann Oncol*. Published online October 17, 2025. doi:10.1016/j.annonc.2025.10.005

MONARCHE: DRFS

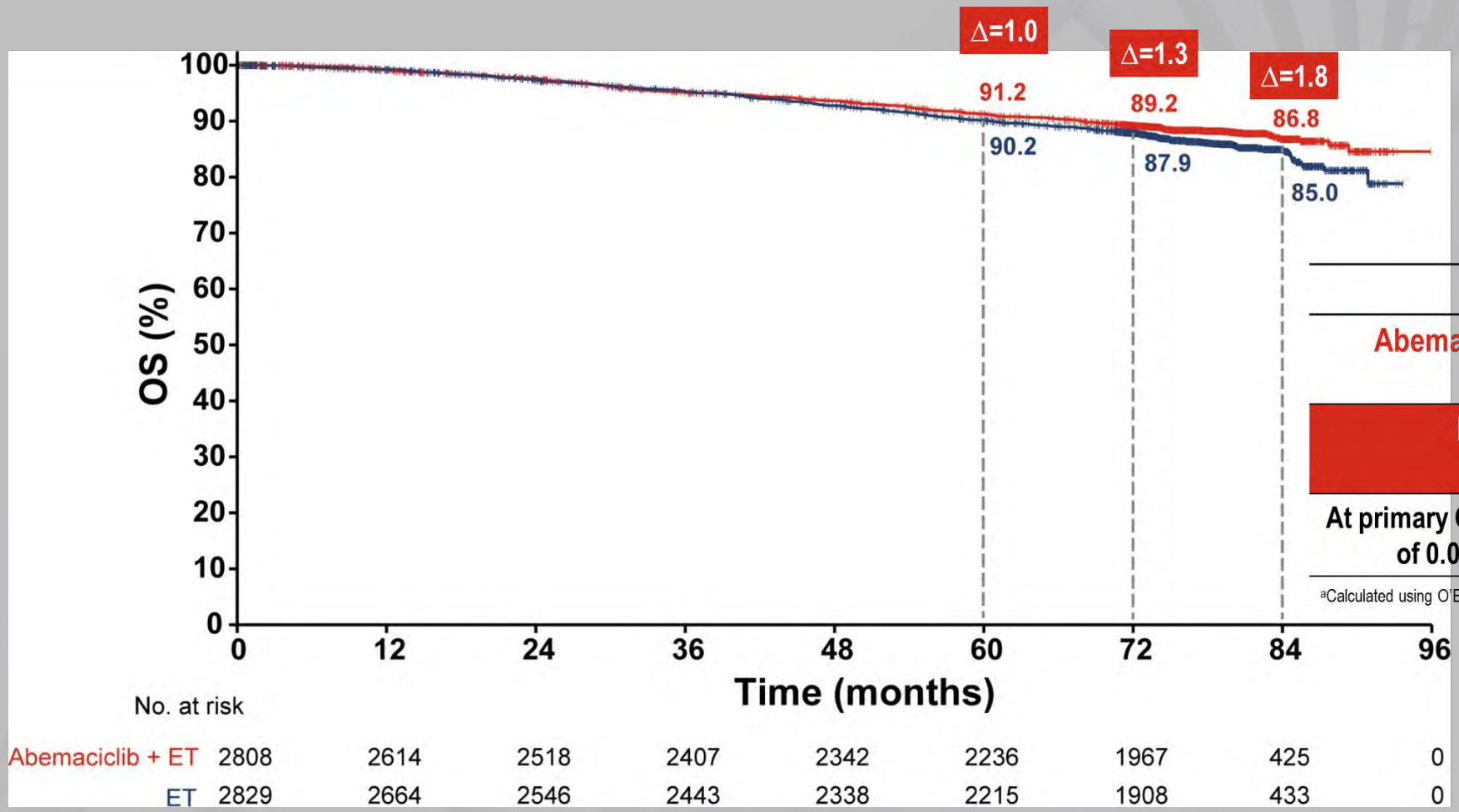


Number of DRFS events	
Abemaciclib + ET	ET
476	621

HR (95% CI): 0.746 (0.662, 0.840)
Nominal *P*<.0001

Johnston S, et al. ESMO 2025. Abstract LBA13. Johnston S, et al. *Ann Oncol.* Published online October 17, 2025. doi:10.1016/j.annonc.2025.10.005

MONARCHE: OVERALL SURVIVAL



Number of OS events

Abemaciclib + ET	ET
301	360

HR (95% CI): 0.842 (0.722, 0.981)
***P*=0.0273**

At primary OS testing, OS in ITT met the critical boundary of 0.0434 (2-sided)[a] for statistical significance

[a]Calculated using O'Brien-Fleming type stopping boundary based on the observed number of events

Johnston S, et al. ESMO 2025. Abstract LBA13. Johnston S, et al. *Ann Oncol*. Published online October 17, 2025. doi:10.1016/j.annonc.2025.10.005

CASE EXAMPLE

- A 65yo female undergoes upfront surgery for a grade 1 ER+PR+HER2- ILC
- Final pathology shows a 4.3cm tumor with 4/9 involved nodes (largest node with 7mm of involvement, no extranodal extension)
- Staging scans are negative for distant disease
- She completes chemotherapy and radiation and presents to your office to finalize her decisions about adjuvant endocrine therapy

- You recommend initiation of anastrozole and also discuss adjuvant abemaciclib with her
- She was expecting to require an aromatase inhibitor, but is taken aback by the idea of an additional two years of treatment that could involve neutropenia, diarrhea, and frequent lab checks

ABEMACICLIB DOSING AND TOLERABILITY: THE TRADE STUDY

- In the monarchE study:
  - 18.5% of patients discontinued for adverse events (mostly diarrhea)
  - 43.5% of patients required dose reduction

- **The TRADE study**: a prospective, single-arm, phase 2 study evaluating **whether a dose-escalation strategy of adjuvant abemaciclib improves drug tolerability** (NCT 06001762)

- 89 evaluable patients (52% stage III/48% stage II) started abemaciclib 50mg BID x 2 weeks→100mg BID x 2 weeks→150mg PO BID onwards
  - Escalation required absence of ongoing g3/4 or persistent g2 toxicity; antidiarrheal medications were allowed
  - **Primary endpoint at 12 weeks** = rate of discontinuation of abemaciclib for any reason, or inability to reach or maintain the 150 mg dose
  - Hypothesis was that this strategy might reduce this rate below 40%

Ann Oncol 2022;33:616-627; Ann Oncol 2026 Jan;37(1):117-124.

TRADE STUDY RESULTS

- 26 patients (29.2%; 90% CI [21.3-38.2]; p=0.046) met the composite endpoint at 12 wks
  - 6 patients discontinued treatment early (3 for toxicity)
  - 8 were unable to reach 150mg; 12 had to dose reduce after initially titrating up to 150mg
  - However, 93.3% continued on therapy at 12 weeks

- The most frequent grade 2 or higher treatment-related AEs by 12 wks:
  - Diarrhea (26.7%), Neutropenia (24.4%), Fatigue (22.2%)
    - Rates of grade 2 or higher diarrhea within 0-4,4-8, and 8-12 weeks were 8.9%,19.1%,16.5% respectively; lower than the 20.5%, 12.1%, 7.3% seen in monarchE in the same periods.

- This dose escalation strategy allowed a greater number of patients (70.8%) to reach and maintain the 150 mg dose at 12 wks than in monarchE, and could be considered in the real world

Ann Oncol2026 Jan;37(1):117-124.

SOME THOUGHTS FROM THE TRENCHES…

- Mention the ‘opportunity’ of the adjuvant CDK 4/6 inhibitor at the beginning of your relationship with the patient

- Consider initiation at 100mg instead of 150mg dose, and explain to the patient that you are doing this to mitigate toxicity (and can titrate up if well tolerated and further down, if not)
  - Helps to build trust and establish rapport

- Reassure patients that if they cannot complete the two years of therapy for any reason, they still get benefit from completing part of it – and that an aromatase inhibitor itself is still very good treatment

What about adjuvant CDK 4/6i for more moderate-risk patients?

NATALEE TRIAL: ADJUVANT ET +/- RIBOCICLIB

Adult patients with stage II and III HR+/HER2− EBC

- Prior ET allowed up to 12 months
- **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

R
1:1[c]

RIB
400 mg/day
3 weeks on/1 week off for **3 y**
+
NSAI
Letrozole or anastrozole[b] for **≥ 5 y**
+ goserelin in men and premenopausal women

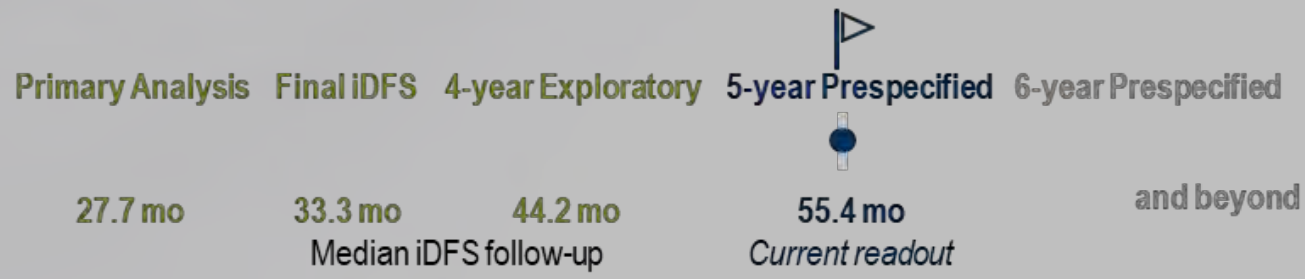
NSAI
Letrozole or anastrozole[b] for **≥ 5 y**
+ goserelín in men and premenopausal women

Primary End Point
IDFS using STEEP criteria

Secondary End Points
- RFS, DDFS, OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- DRFS
- Gene expression and alterations in tumor ctDNA/ctRNA samples

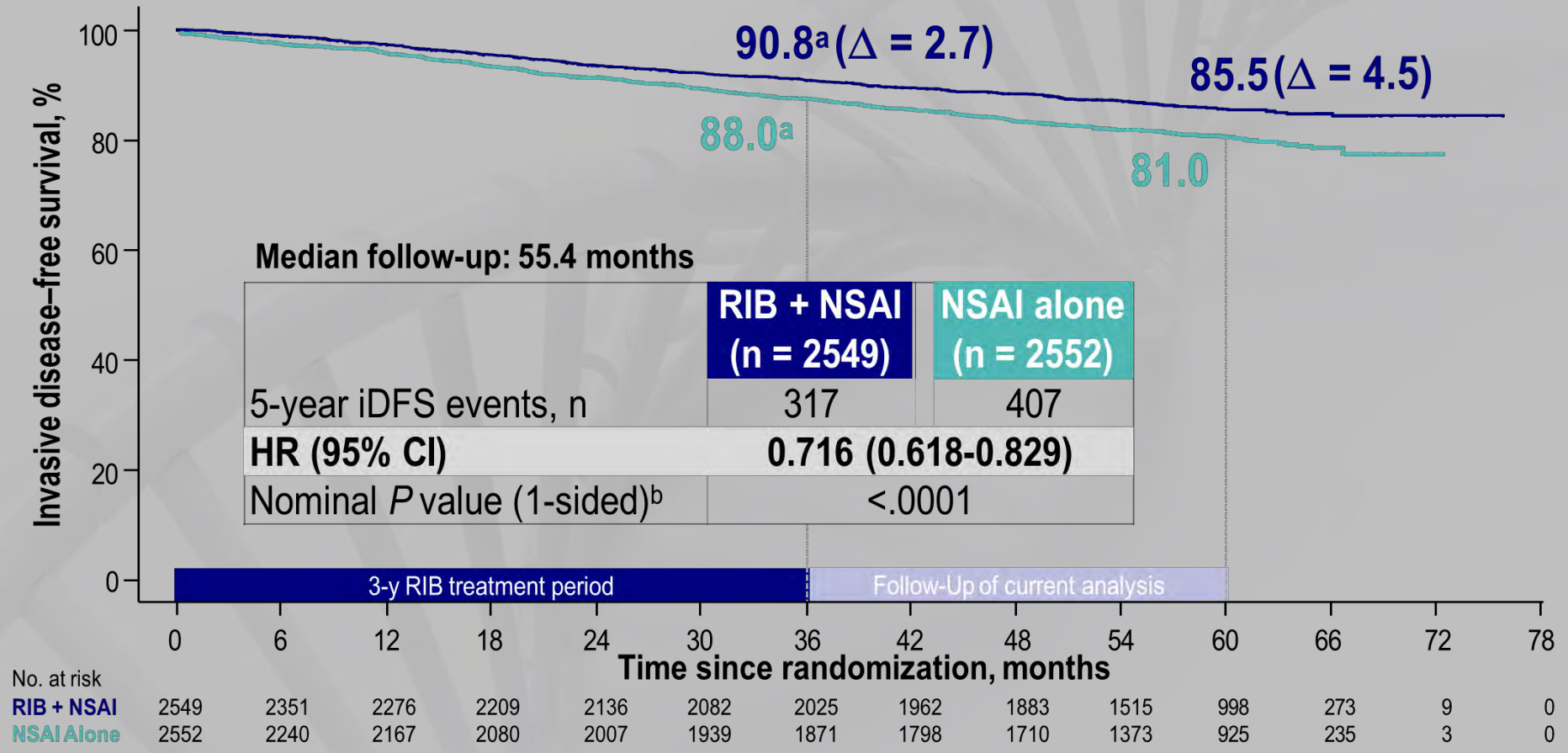
Efficacy outcomes for the 5-year analysis were estimated by the Kaplan-Meier method, and results are descriptive. The Cox proportional hazards model was used to estimate the HRs and 95% CIs.



[a]Enrollment of patients with stage II disease was capped at 40%. [b]Per investigator choice.

Crown J, et al. ESMO 2025. Abstract LBA14. Crown J, et al. *ESMO Open*. Published online October 17, 2025. doi:10.1016/j.esmoop.2025.105858

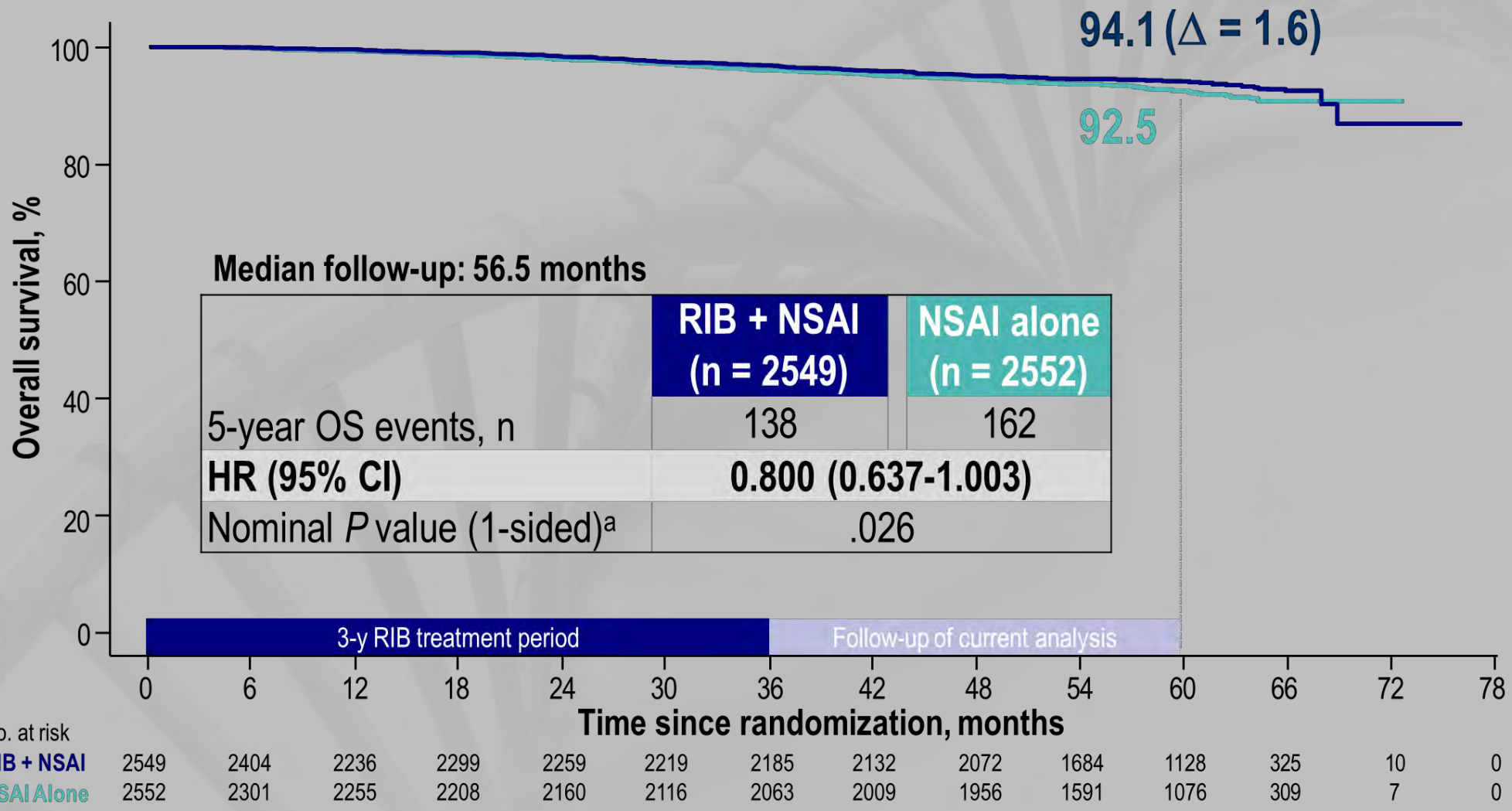
NATALEE: IDFS



[a]The difference between percentages does not equal 2.7 due to rounding.[b]Comparison of survival between treatment arms was generated by stratified log-rank test (1-sided *P* value, informational and not preplanned).

Crown J, et al. ESMO 2025. Abstract LBA14. Crown J, et al. *ESMO Open*. Published online October 17, 2025. doi:10.1016/j.esmoop.2025.105858

NATALEE: OS



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Crown J, et al. ESMO 2025. Abstract LBA14. Crown J, et al. *ESMO Open*. Published online October 17, 2025. doi:10.1016/j.esmoop.2025.105858

CASE EXAMPLE

- A 42yo woman who underwent mastectomy for a T2N1 ER+PR+HER2- breast cancer in 2023 (2.2cm grade 2 disease, one positive node) followed by chemotherapy comes in for follow-up. She started letrozole/OFS after surgery, and started 400mg ribociclib daily 15 months ago (very soon after its approval).

- In the office today, she is tearful, explaining that she has not taken her medication for the last 8 weeks because she is ‘so tired of feeling tired’ and depressed.
  - Symptoms have been much better off endocrine therapy

- After discussion, she agrees to go back on endocrine therapy with ribocicilb at 200mg daily for now, and to see her back in six weeks. You also connect her with a therapist.

ADVERSE EVENT MANAGEMENT AND ADHERENCE

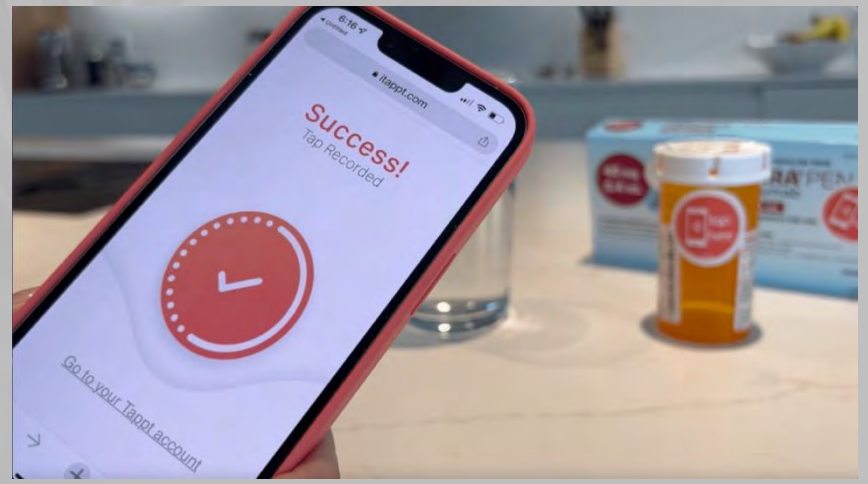
- The shift from intravenous therapies to mostly oral regimens has allowed flexibility for patients and largely improved quality of life, in addition to optimizing cancer-related outcomes

- However, it is critical that we give patients all the tools they need to optimize adherence since we are no longer guaranteeing this by administering these medications in clinic

- **Adherence** to oral CDK 4/6 inhibitors is a critical part of optimizing effectiveness of these agents

HARNESSING TECHNOLOGY?

- At Emory, we studied the Tappt app to determine feasibility and usability of this system in women with breast cancer prescribed a CDK 4/6i
- Patients used the app to record dosing for 3 months and received missed dose reminders and reminders to report symptoms biweekly
- Alerts were sent to oncology teams for nonadherence (>20% missed doses) or moderate-to-severe symptoms.



- 107 patients were studied, and mean CDK 4/6i adherence, with the use of the app, was 92.8%
- Anxiety and depression were associated with lower adherence rates to medication

JCO Clin Cancer Inform. 2025 Nov: 9e2500152

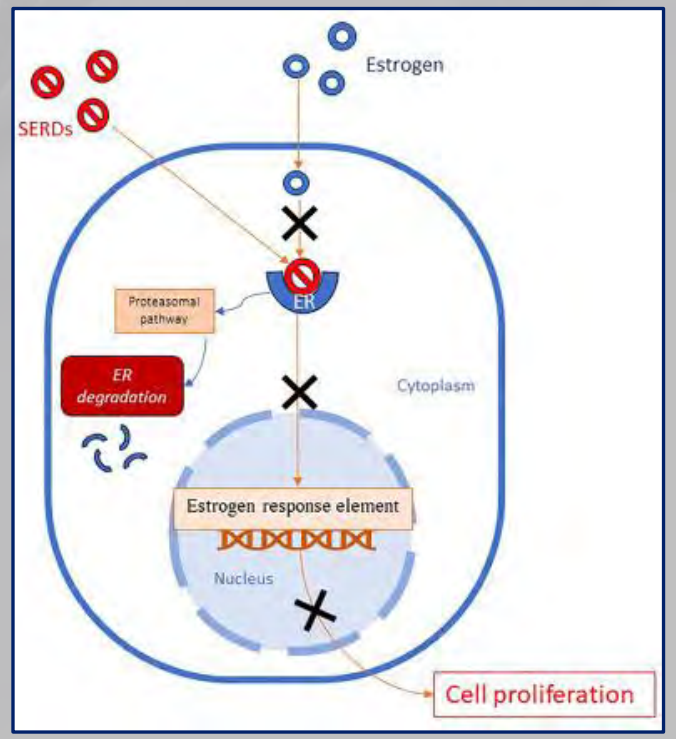
PROGRESSION AND ESR1 MUTATIONS

- Roughly 20-40% of patients with ER+ breast cancer develop distant metastases, with half of these events occurring 5+ years after initial diagnosis

- Some recurrences happen because of the development of ESR1 mutations
  - These change the shape of the ER, locking it into an ‘on’ position without the need to bind to estrogen
  - Thus, the ER signals the cancer cell to grow whether or not there is estrogen around to feed it

- SERDs (serum estrogen receptor downregulators) to target this resistance mechanism have proven useful in the metastatic setting
  - Imlunestrant, elacestrant approved for *ESR1m* HR+ mBC

- They are now being studied in patients with early stage disease



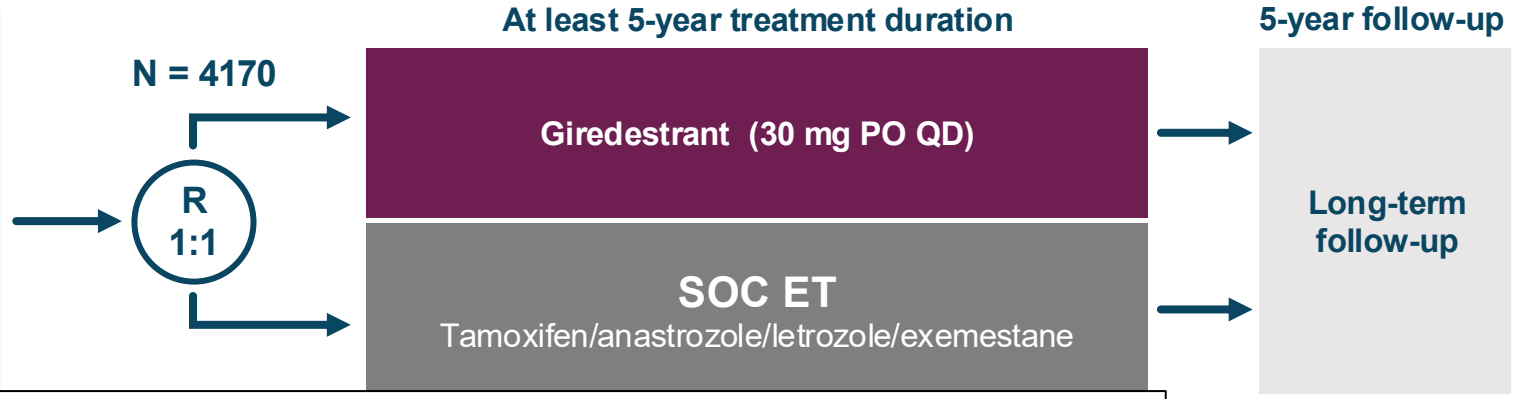
Guglielmi G et al. Eur J Pharmacol. 2024

LIDERA BREAST CANCER STUDY DESIGN

A GLOBAL, RANDOMIZED, OPEN-LABEL, MULTICENTER PHASE III TRIAL

Key Eligibility Criteria

- Participants with ER+, HER2-negative early breast cancer
- Stage I–III disease (anatomical)
  - pN0 and pT > 1 cm with Grade 3, or Ki67 ≥ 20%, or high score on genomic assay,* or pT4N0
  - Node-positive
- Pre- or post-menopausal†
- Breast cancer surgery within 12 months



Medium risk (~30.5% of trial patients)

- pN0 and T >1 cm with high-risk features (G3, or Ki67 ≥ 20%, or high genomic score)
- pN1 with low-risk features (G1/2 and Ki67 < 20% and tumor ≤ 5 cm and low genomic score).

High risk (~69.5% of trial patients)

- pT4
- pN2-3
- pN1 with high-risk features (G3, or Ki67 ≥ 20%, or tumor > 5 cm, or high genomic score).

Ultimately in the trial, just over 20% were pN0 and ~13% stage I

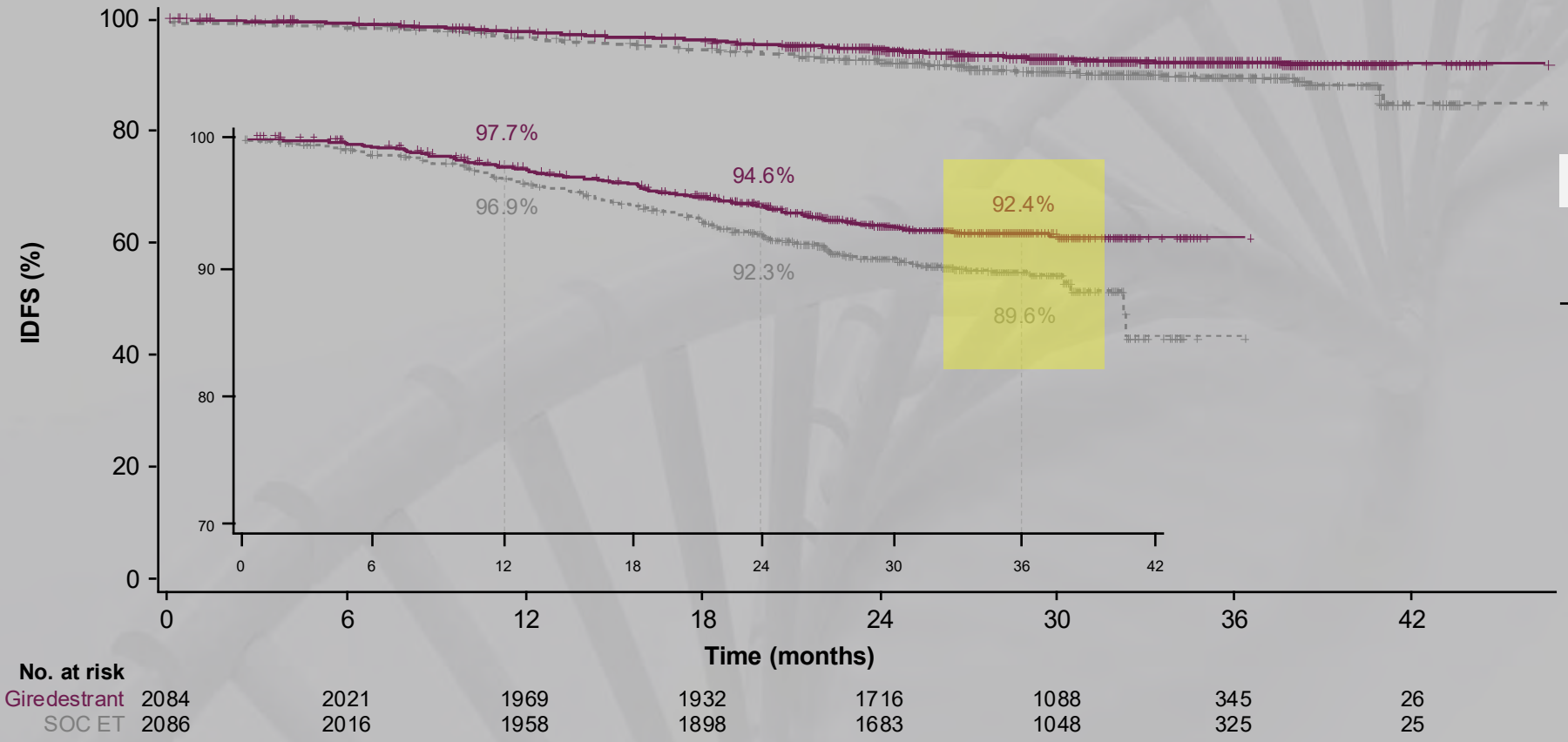
cer with exception of
FI, OS, safety

ly 1)

risk Mammaprint.
risk: pN0 and primary tumor
≤ 5 cm and low score on genomic

assay [if available]). § High risk: pT4, or pN2, or pN3 and pN1 with high-risk biologic features (Grade 3, or Ki67 ≥ 20%, or tumor > 5 cm, or high score on genomic assay [if available]).
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DFS, disease-free survival; DRFI, distant recurrence-free interval; ER+, estrogen receptor-positive; ET, endocrine therapy; IDFS, invasive disease-free survival; LRRFI, locoregional recurrence-free interval; OS, overall survival; PO, orally; QD, once daily; R, randomization; RoW, rest of the world; SOC, standard-of-care.
ClinicalTrials.gov number, NCT04961996. Adapted from Geyer CE, *et al*. ASCO 2023 (TPS616), with permission.

LIDERA PRIMARY ENDPOINT: IDFS



	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	140 (6.7)	196 (9.4)
Stratified HR (95% CI)	**0.70** (0.57, 0.87); **p = 0.0014***	

Median f/u 32 months

- **Early separation of curves**
- **Absolute benefit 2.8%**

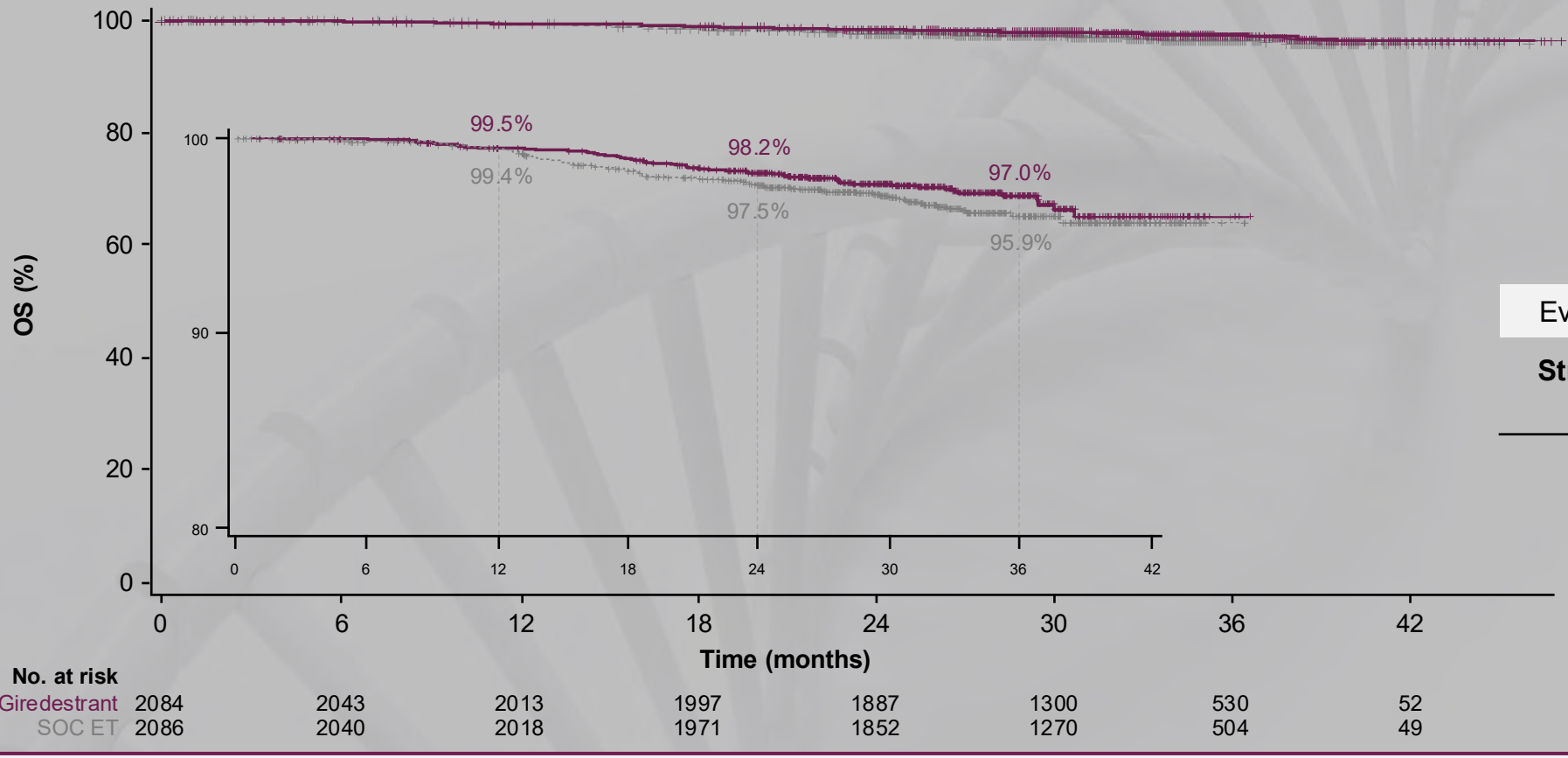
Median follow-up: 32.3 months

Statistically significant and clinically meaningful improvement in IDFS:
Giredestrant reduced the risk of invasive disease recurrence or death by 30% compared with SOC ET

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. * Log-rank (2-sided). p-value boundary for IDFS interim analysis was 0.0217 (2-sided). AI, aromatase inhibitor; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care.

Presented by: Aditya L. Bardia, MD. SABCS 2025

LIDERA: INTERIM OVERALL SURVIVAL



	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	57 (2.7)	71 (3.4)
Stratified HR (95% CI)	**0.79** (0.56, 1.12); p = 0.1863*	

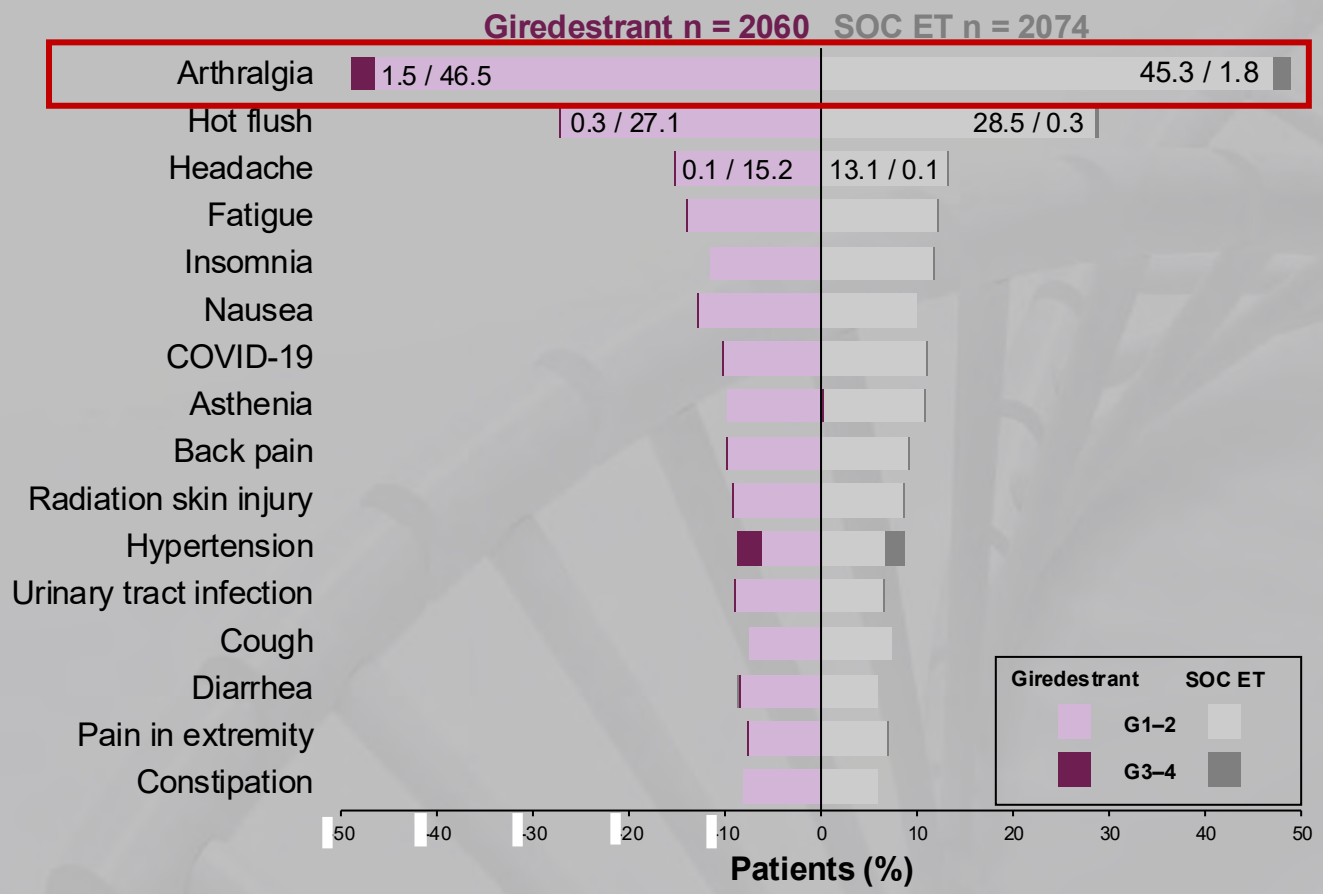
Median follow-up: 32.3 months

While OS data were immature, a clear positive trend was observed. OS testing will continue at future analyses

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. At the data cutoff, the 1st OS IA was conducted (maturity 31.2% with respect to the final OS analysis). * Log-rank (2-sided). p-value boundary for the 1st OS IA was 0.0001 (2-sided). Includes one death from a patient who was randomized but never dosed. Excludes one death from a patient with missing date of death. CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IA, interim analysis; OS, overall survival; SOC, standard-of-care.

LIDERA AE OVERVIEW

Common TEAEs (≥ 7.5% of patients in either arm at any grade)



Selected AEs

	Giredestrant n = 2060	SOC ET n = 2074
Patients, n (%) with treatment discontinuations due to AEs		
Musculoskeletal disorders	38 (1.8)	92 (4.4)
• Arthralgias (PT)	32 (1.6)	76 (3.7)
Vasomotor disorders	2 (< 0.1)	18 (0.9)
• Hot flush (PT)	1 (< 0.1)	16 (0.8)

	Giredestrant n = 2060			SOC ET n = 2074		
Patients, n (%) with selected AEs by medical concept*						
	G1	**G2**	**G3–4**	**G1**	**G2**	**G3–4**
Bradycardia†	217 (10.5)	15 (0.7)	0	64 (3.1)	2 (< 0.1)	0
Venous thromboembolic events	4 (0.2)	12 (0.6)	2 (< 0.1)‡	3 (0.1)	7 (0.3)	7 (0.3)

Data cutoff: August 8, 2025. * Assessed as medical concepts using grouped terms; all other AEs by medical concept were comparable between arms, including four patients per arm (0.2%) who experienced photopsia. † G2 events occurred in 17 patients; 13 resolved, four patients discontinued treatment and the events resolved.‡ G3 only. AE, adverse event; ET, endocrine therapy; G, grade; PT, preferred term; SOC, standard-of-care; TEAE, treatment-emergent adverse event.

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THE FUTURE OF ORAL SERDS IN THE ADJUVANT SETTING

- lidERA had a similar PFS benefit at 3 years as was seen with adjuvant CDK 4/6i; if approved, could it replace these agents in certain populations?
  - Limitations: not studied alongside adjuvant CDK 4/6i, which has longer follow-up in patients who qualify
  - Cost could also be a factor

- NOVEL TRIALS/THERAPEUTIC STRATEGIES:

Trial	NCT #	Drug Class	Study Design	Patient population
CAMBRIA-1	05774951	Oral SERD	Camizestrant vs standard ET	High-risk EBC after 2-5y standard ET
CAMBRIA-2	05952557	Oral SERD	Cami vs standard ET (both +/- abemaciclib)	High-risk EBC at the beginning of endocrine therapy
EMBER-4	05514054	Oral SERD	Imlunestrant vs standard ET	High-risk EBC after 2-5y standard ET
ELEGANT	06492616	Oral SERD	Elacestrant vs standard ET	High-risk EBC after 2-5y standard ET

CONCLUSIONS

- In early stage HR+ breast cancer, treatment options are complex, and **integrating our understanding of a patient's disease biology with the patient's personal goals and medical history** allows us to help patients make the best possible decisions

- Five years of endocrine therapy remains the backbone of treatment, with **consideration of extended ET and CDK 4/6i for higher-risk patients**
  - Abemaciclib (2y) or ribociclib (3y) are now SOC opportunities for patients with high-risk early stage disease
    - Consider dose reductions to mitigate side effects and/or starting at a lower dose and titrating up

- **Future considerations**
  - Giredestrant for certain subset of patients?
  - Other adjuvant SERD trials could potentially change practice
  - Potential future role for monitoring ctDNA

- Managing side effects proactively and ensuring that mental health providers, nutritionists, pharmacists, and other professionals are available can be critical to optimizing compliance with and effectiveness of therapy

QUESTIONS?

Module 10: HR-Positive Breast Cancer

Current and Future Management of HR-Positive, HER2-Negative Localized Breast Cancer — Dr Meisel

Optimizing First-Line Therapy for Patients with HR-Positive mBC — Dr Hamilton

Current and Future Role of Oral SERDs for Progressive HR-Positive mBC — Dr Wander

Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr O'Shaughnessy

Optimizing 1L therapy for HR+ MBC

Erika Hamilton, MD

Chief Development Officer, Late Phase

Director, Breast Cancer Research Program

Sarah Cannon Research Institute

Nashville, TN, USA

SCRI Sarah Cannon Research Institute

April 26, 2026

Disclosures

Consulting/Advisory Roles (All Payments to Institution)	Accutar Biotechnology Inc, Arvinas, AstraZeneca Pharmaceuticals LP, BeOne, Circle Pharma, Daiichi Sankyo Inc, Entos Pharmaceuticals, Genentech, a member of the Roche Group, Gilead Sciences Inc, Halda Therapeutics, Incyclix Bio, IQVIA, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Jefferies LLC, Johnson & Johnson, Lilly, Medical Pharma Services SRO, Mersana Therapeutics Inc, Novartis, Pfizer Inc, Pyxis Oncology, Samsung Bioepis, Shorla Oncology, Stemline Therapeutics Inc, Tempus, Zentalis Pharmaceuticals
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Nonrelevant Financial Relationships	Dana-Farber Cancer Institute

CDK4/6i + ET as 1L therapy for HR+/HER2- MBC

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Efficacy with 1L CDK4/6i +ET

Study name	Treatment	CDK4/6i mPFS (months)	Placebo mPFS (months)	Δ PFS (months)	HR, P value	CDK 4/6i mOS (months)	Placebo mOS (months)	Δ OS (months)	HR, P value/ 95% CI
PALOMA-2	Palbociclib/ Placebo + Letrozole	27.6	14.5	13.1	0.56, p<0.0001	**53.9**	**51.2**	**2.7**	0.96 (95% CI, 0.78-1.18)
MONALEESA-7	Ribociclib/ Placebo + AI/Tam + OFS	23.8	13	10.8	0.553, p <0.001	**58.7**	**48**	**10.7**	0.76 (95% CI, 0.61-0.96)
MONALEESA-2	Ribociclib/ Placebo + Letrozole	25.3	16	9.3	0.568, $p=9.63x10^{-8}$	**63.9**	**51.4**	**12.5**	0.76 p=0.004
MONARCH-3	Abemaciclib+ NSAI vs Placebo +NSAI	28.2	14.8	13.4	0.54, p=0.000021	**67.1**	**54.5**	**12.6**	0.75, p=0.03 (IA)

Slamon DJ et al. JCO 2024;
Hortobagyi GN et. al NEJM 2022;
Goetz M et al JCO 2017

RIGHT Choice trial: 1L CDK4/6i+ET or Chemotherapy?

- ER+ and/or PgR+/HER2- MBC
- Age 18-60
- Indication for aggressive Tx:
  - Symptom. visceral mets,
  - Rapid PD or
  - Impending visceral crisis

N = 222 patients

Stratification :
- DFI (</>2 yrs)
- Liver metastases

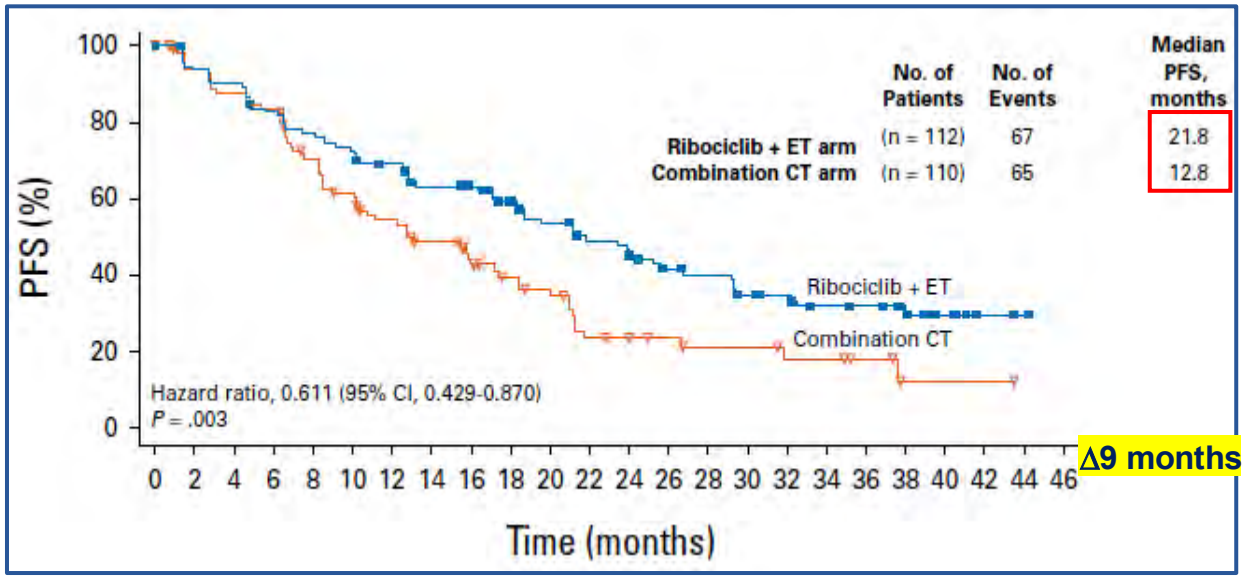
ET+ Ribociclib

Combination Chemotherapy

Docetaxel/Capecitabine, Paclitaxel/Gemcitabine, Capecitabine.VInorelbine

Study was conducted primarily in Asia, Africa, Egypt, Eastern EU primarily where chemo is usually given as first line therapy for these patients

Final PFS after median follow up of 37 months



Patient Population:

De novo MBC 64%	Sympt visceral mets 68%
DFI >2 yrs 25%	Rapid PD 18%
Metastatic sites ≥3 56%	Lung/liver mets 76%

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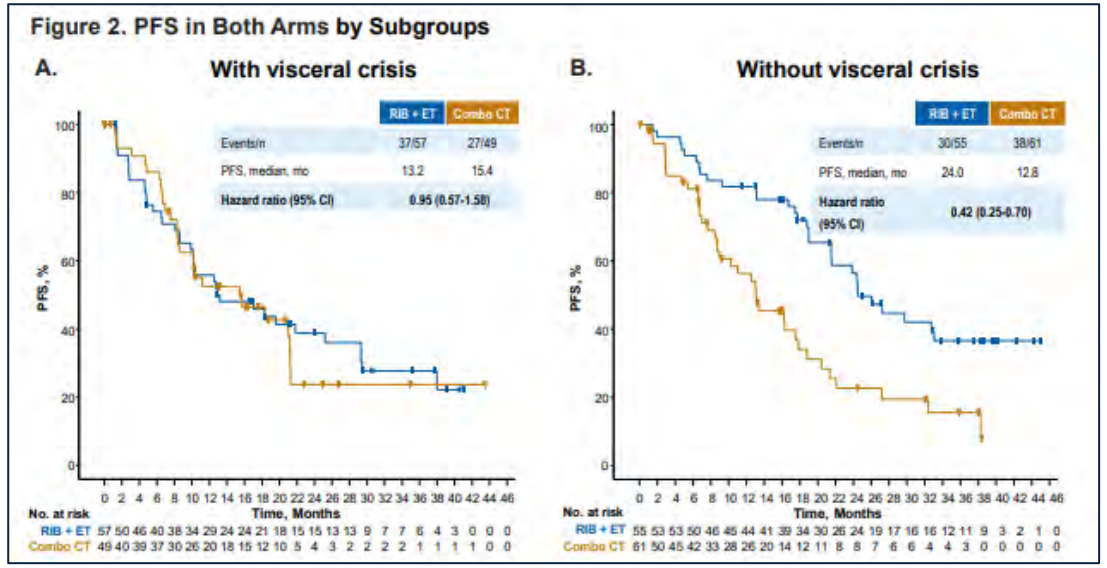
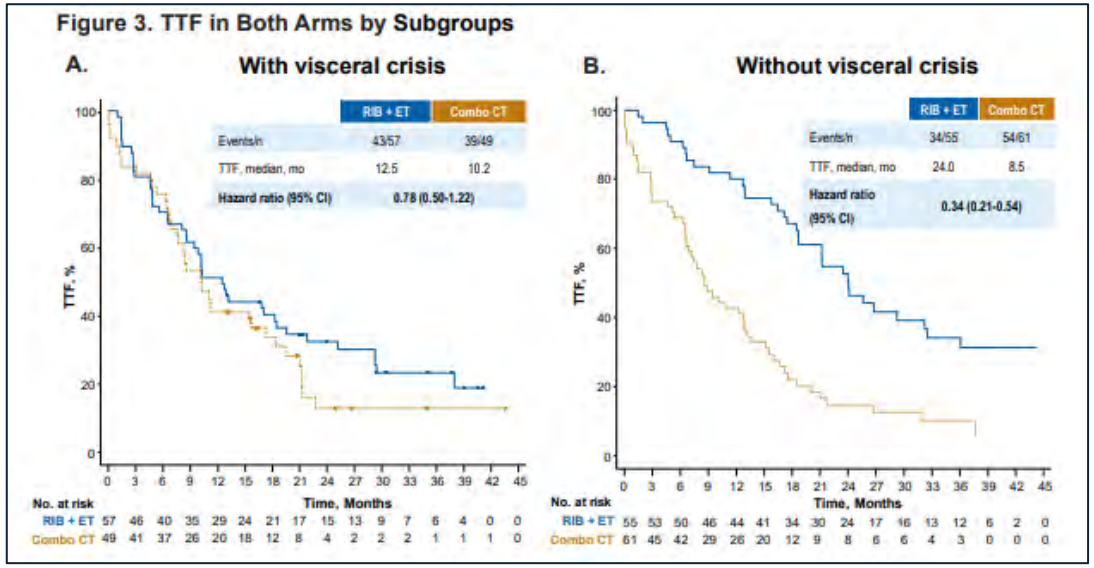
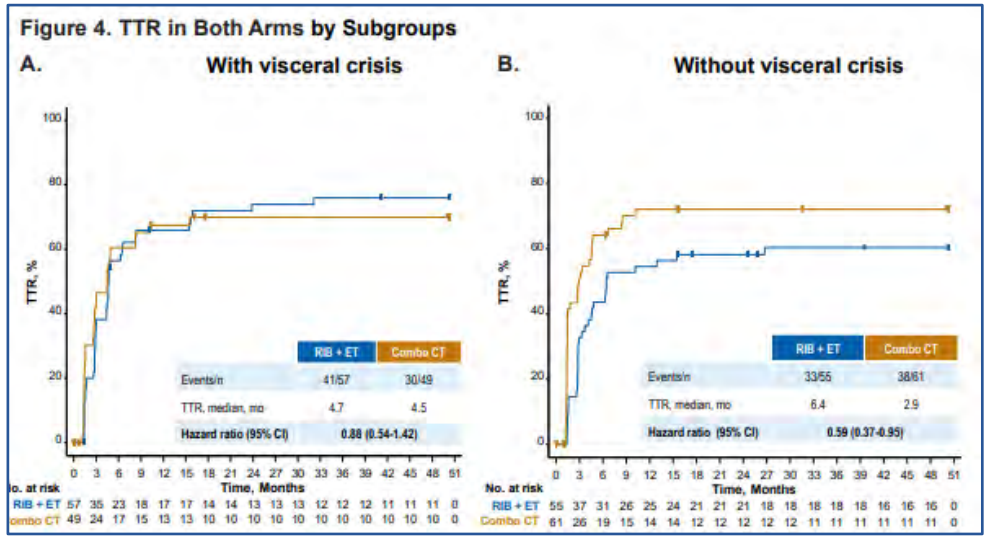
Lu Y-S et al JCO 2024

RIGHT Choice: Subgroup analysis







Ribociclib+ET is as effective if not superior to combination chemotherapy based on PFS, TTF, TTR and ORR

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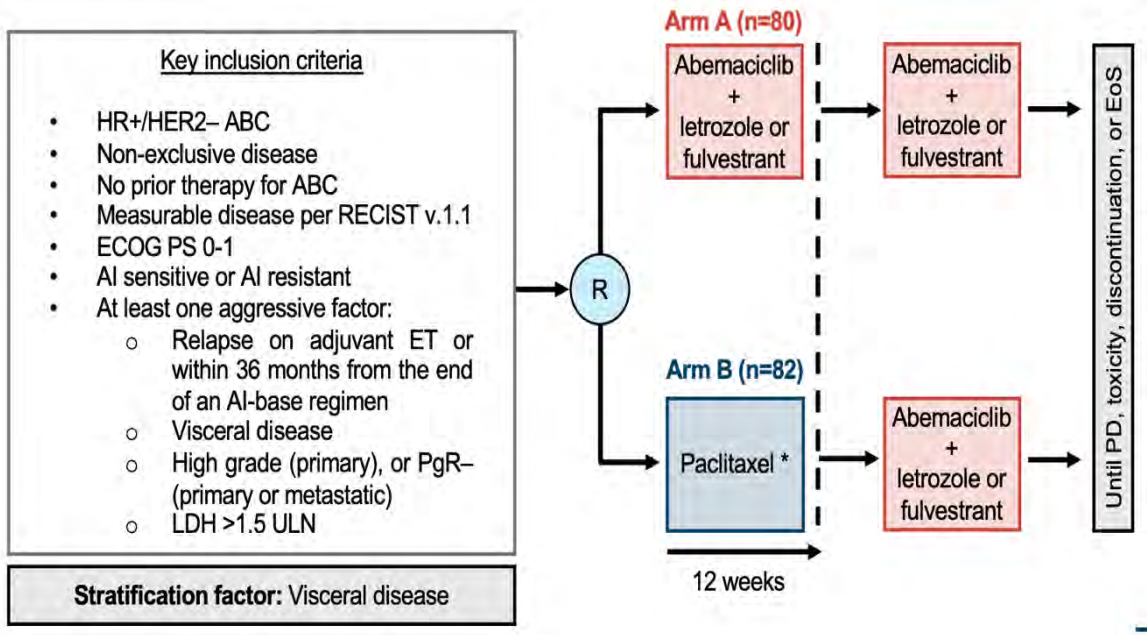
Azim HA et al. ESMO 2023 402P.

ABIGAIL: Non inferiority trial of abema+ET +/- induction chemo in untreated HR+/HER2- MBC



The primary endpoint was met with a12-week ORR per BICR of 58.8% in abemaciclib+ET, and 40.2% in paclitaxel (p=0.0193)

Efficacy data

	Abemaciclib + ET N = 80	Paclitaxel N = 82	Odds ratio (95%CI); p value
12-week ORR in ITT population			**2.11 (1.13-3.96)' 0.0193**
Complete response, partial response	47 (58.8%)	33 (40.2%)	
Stable disease, progressive disease , or discontinuation	33 (41.2%)	49 (59.8%)	
Response at 12 weeks since randomization			
Complete response	0 (0%)	0 (0%)	
Partial response	47 (58.8%)	33 (40.2%)	
Stable disease	24 (30.0%)	37 (45.2%)	
Progressive disease	1 (1.2%)	7 (8.5%)	
Not evaluable	8 (10.0%)	5 (6.1%)	
Death*	2 (2.5%)	2 (2.4%)	
Withdrawal of consent	2 (2.5%)	1 (1.3%)	
Toxicity	2 (2.5%)	0 (0%)	
Non-radiological progression	1 (1.25%)	0 (0%)	
Incorrect randomization	1 (1.25%)	2 (2.4%)	

*Deaths were due to causes different from treatment-related toxicity.

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Haba-Rodríguez J et al. ESMO 2024

AMBRE: 1L trial of chemo vs Abema+ET

- ER+ HER2- ABC
- No prior treatment for ABC
- High tumor burden
  - ≥2 visceral sites
  - or ≥ 3 lesions in 1 visceral site
  - or 1 visceral site & high LDH

N=180

R

Chemotherapy (CT)
- capecitabine
- paclitaxel

+ maintenance ET + abemaciclib allowed

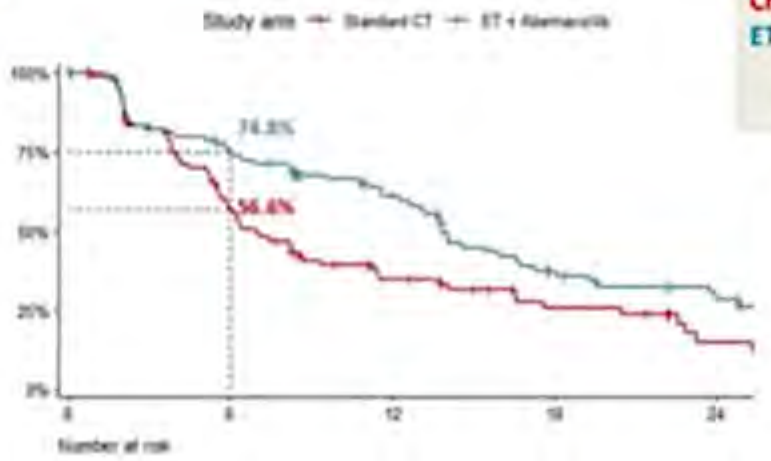
Endocrine Therapy (ET)
- NSAI
- fulvestrant

combined with abemaciclib

Stratification factors
- **ET sensitivity**
  - *de novo* stage IV
  - relapse >1y after adjuvant ET
  - relapse during or <1y after adjuvant ET
- **Planned CT**: capecitabine vs paclitaxel
- **Liver metastasis**: present vs absent

CTC count

Progression-Free Survival



	Median PFS (95% CI)
Chemotherapy	7.0 mths (5.6-9.4)
ET+ Abemaciclib	13.9 mths (11.5-16.8)

Stratified HR=0.67 (0.46-0.98) p=0.035

ORR: 29.2% vs 35.2% NS (p=0.4)
DoR: 7.4 mths vs 10.9 mths
HR=0.46 (0.24-0.90), p=0.023

Median FU of 26.2 mths (95% CI 22.7 to 28.8)

Third study to demonstrate that CDK4/6i +ET is an appropriate 1L treatment option even in patients with high tumor burden

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Marques CE et al SABCS 2025

Oral SERDs as 1L therapy for HR+/HER2- MBC

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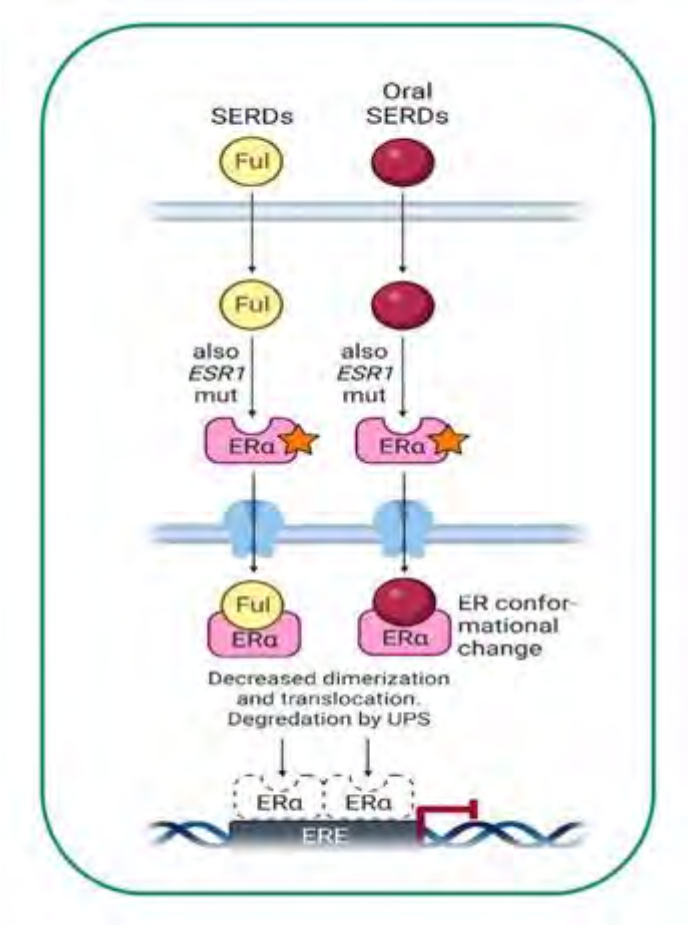
New Oral SERDs



Oral SERDs offer several advantages over conventional ET

- Oral bioavailability
- High potency
- Activity against *ESR1* mutant ER
- Less toxicity
- Demonstrated efficacy in pretreated HR+/HER2- MBC

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Figure adapted from C. Corti Cancer Treatment Reviews 2023

SERENA-6: 1L trial of ctDNA guided early switch study for HR+/HER2- MBC

- *ESR1* mutations are detected in ~40% of patients treated with 1L CDK 4/6i+AI
- Camizestrant, an oral SERD significantly improved PFS vs fulvestrant in pretreated HR+/HER2- MBC including pts with *ESR1* mutations

Will using camizestrant to treat emerging *ESR1* mutations ahead of disease progression extend the duration of benefit of 1L CDK4/6i + AI?

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

→ R 1:1
N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Stratification factors

- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

Continuing AI (anastrozole/ letrozole) + CDK4/6i + placebo for camizestrant

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints

- PFS2**
- OS**
- Safety
- Patient-reported outcomes

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Turner NC et al. ASCO 2025

SERENA-6: Patient characteristics

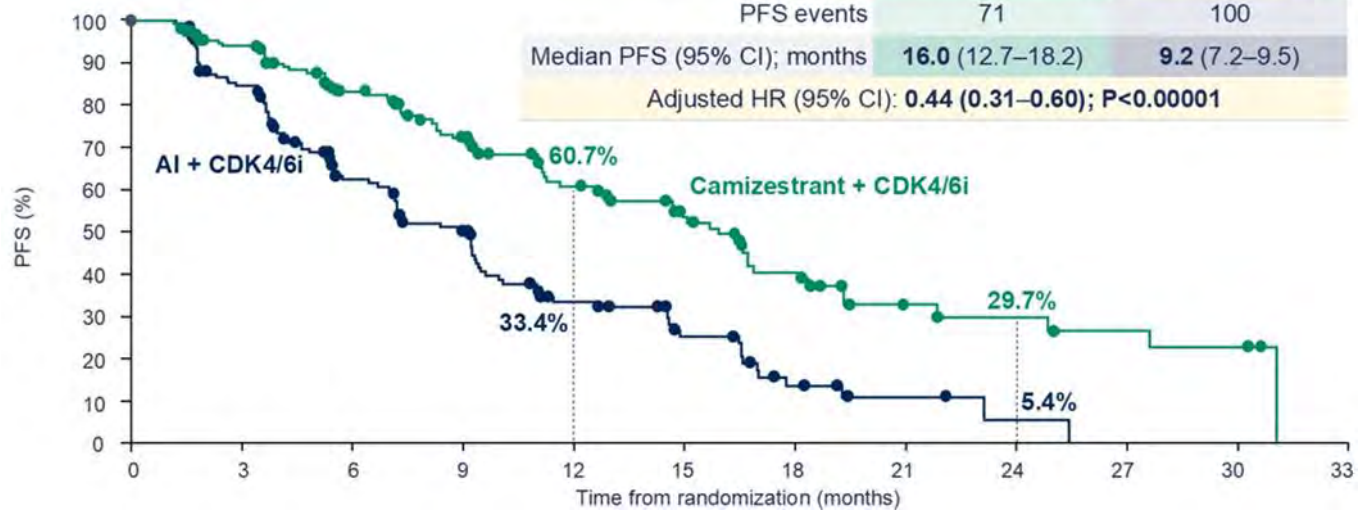
Characteristic		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Median age (range) — years		61.0 (29–81)	60.5 (35–89)
Female — n (%)		157 (100)	155 (98)
Race — n (%)	White	97 (62)	102 (65)
	Asian/other	39 (25) / 21 (13)	34 (22) / 22 (14)
Postmenopausal status — n (%)		123 (78)	127 (80)
ECOG performance-status score — n (%)*	0/1	107 (68) / 48 (31)	98 (62) / 56 (35)
Visceral metastases — n (%)†		66 (42)	71 (45)
Time of *ESR1*m detection — n (%)†	At first test	84 (54)	84 (53)
	At a subsequent test‖	73 (47)	74 (47)
	Median (range) – months	22 (4–95)	22 (6–96)
Time from initiation of AI + CDK4/6i to randomization — n (%)†	≥18 months	97 (62)	100 (63)
	<18 months	60 (38)	58 (37)
	Median (range) – months	23 (7–96)	23 (6–96)
CDK4/6i continued at randomization — n (%)†	Palbociclib	119 (76)	119 (75)
	Ribociclib	24 (15)	23 (15)
	Abemaciclib	14 (9)	16 (10)
Most common *ESR1*m at baseline — n (%)‡	D538G	70 (45)	82 (52)
	Y537S	61 (39)	60 (38)
	Y537N	29 (19)	25 (16)

Turner NC et al. ASCO 2025; Bidard F-C et al. *N Engl J Med* 2025;393(6):569-80.

SERENA-6: Primary and secondary endpoints

Primary EP – Investigator assessed PFS

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		

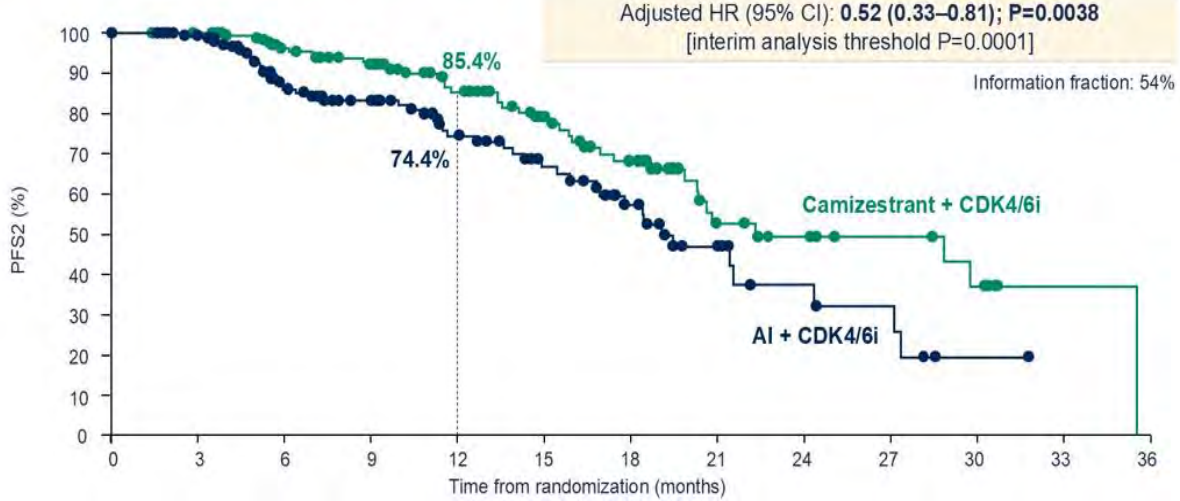


Significant improvement in PFS with switching to camizestrant
All subgroups benefited from switching to camizestrant

Key secondary EP – PFS2

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	38	47
Adjusted HR (95% CI): **0.52 (0.33–0.81); P=0.0038** [interim analysis threshold P=0.0001]		

Information fraction: 54%



No significant improvement in PFS2 between the 2 arms
(HR 0.52, P=0.0038, which was below the IA threshold P=0.0001)

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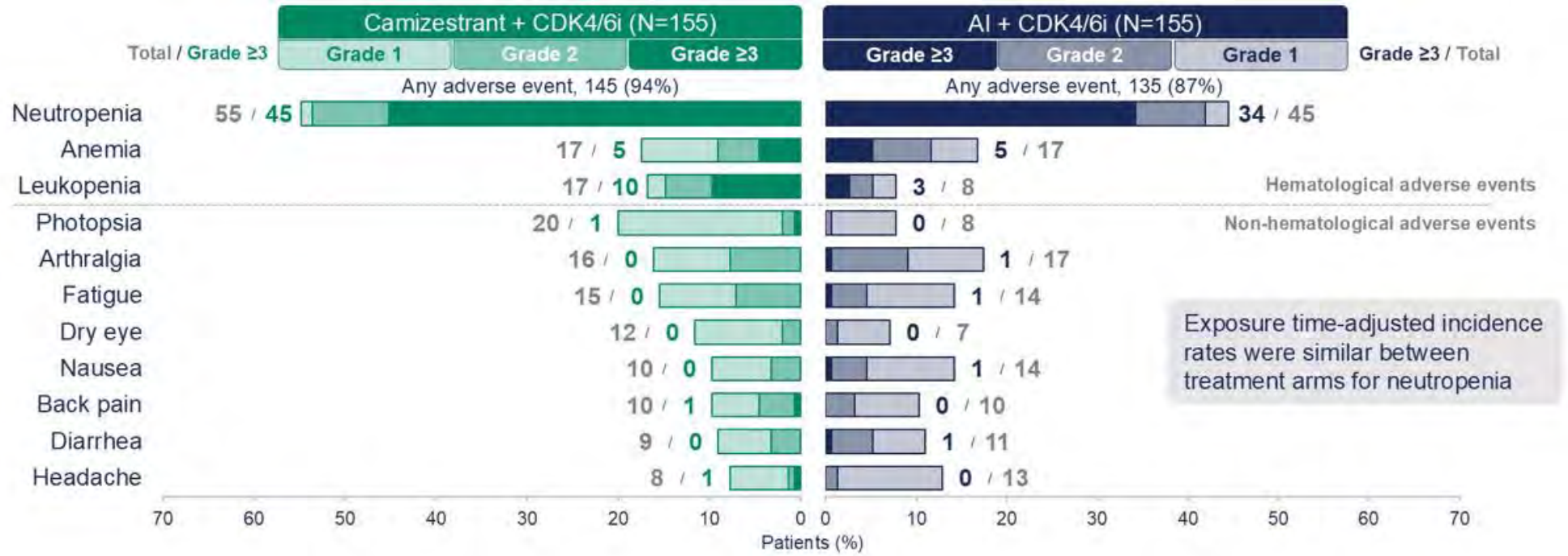
Turner NC et al. ASCO 2025; Bidard F-C et al. *N Engl J Med* 2025;393(6):569-80.

SERENA-6: Adverse Events



Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities: If experienced, visual effects had no/minimal impact on daily activities, were typically ≤1 minute, ≤3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity

Camizestrant + CDK 4/6i was well tolerated with low rates of discontinuation

QoL analysis indicated that Camizestrant + CDK 4/6i delayed time to deterioration in QoL vs continuing CDK 4/6i+AI

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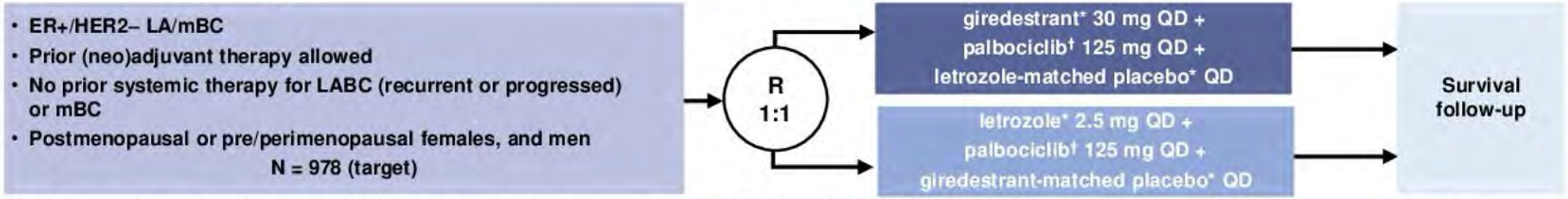
Turner NC et al. ASCO 2025; Bidard F-C et al. *N Engl J Med* 2025;393(6):569-80.

persevERA: Ph 3 trial of 1L giredestrant + palbociclib vs letrozole + palbociclib For HR+/HER2- MBC



Study treatments are administered orally. In addition, men and pre/perimenopausal women will also receive an LHRH agonist. Pts are to continue to receive study treatment until disease progression or unacceptable toxicity. * Day 1–28 of each 28-day cycle. † Day 1–21 of each 28-day cycle.
Stratification factors: Site of disease, disease-free interval since the end of (neo)adjuvant therapy, menopausal status, geographic region.

Sunday, March 8, 2026

Update on Phase III persevErA Study in ER-Positive Advanced Breast Cancer

- persevERA Breast Cancer study did not meet the primary objective of a statistically significant improvement in progression-free survival, but a numerical improvement was observed
- Giredestrant plus palbociclib was well tolerated and adverse events were consistent with the known safety profiles of each individual treatment
- The FDA recently accepted the New Drug Application based on evERA data; Phase III lidERA data will be submitted to the FDA in the coming weeks
- persevERA is the first of two distinct Phase III studies in the first-line setting; pionERA study of giredestrant in combination with physician's choice of CDK4/6 inhibitor in endocrine-resistant ER-positive breast cancer is expected to readout in 2027

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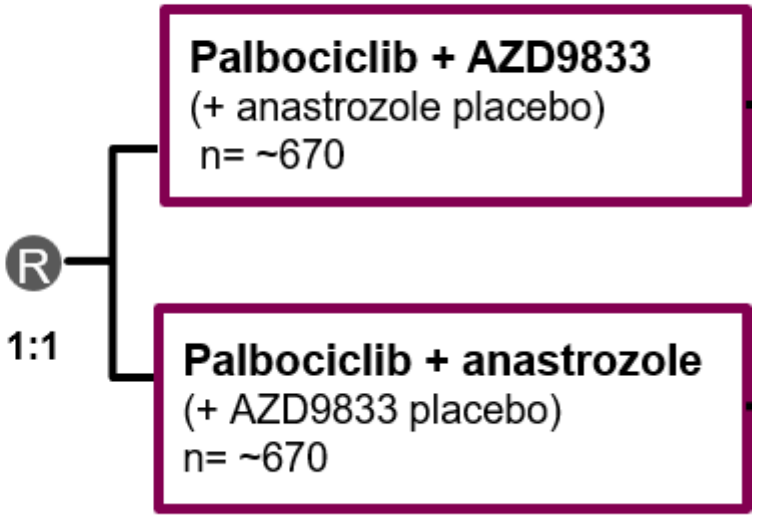
SERENA-4:Ph 3 trial of Palbociclib with camizestrant or anastrozole for 1L HR+/HER2- MBC

Trial completed enrollment; results awaited

- Newly diagnosed metastatic breast cancer patients who have not received any systemic treatment for metastatic disease
  - De Novo
  - Recurrence from early stage disease:
    - at least 24 months of an AI with a TFI > 12 months
    - at least 24 months of TAM (pre-/peri-menopausal)
- Documented ER+ >10%, HER2- disease
- Pre and postmenopausal women and male patients
- PS 0-1

N=1342



Primary endpoint:
PFS

Key secondary endpoints:
OS and PFS2

AZD9833 aka Camizestrant

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Im S-A et al. ASCO 2021;Abstract TPS1101.

pionERA: Trial of giredestrant or fulvestrant with CDK4/6i in endocrine resistant 1L HR+/HER2- MBC

Trial is currently enrolling

N~1050 (420 *ESR1*m [40%], 630 *ESR1*nmd)

- post- or pre/perimenopausal[1] women, men[1]
- ER+ HER2- LA/mBC; confirmed *ESR1* status[2]
- resistant to adjuvant ET (± CDK4/6i): relapse
  - on-treatment after ≥12 mo *OR*
  - off-treatment within ≤12 mo (TFI)
  - if CDK4/6i, ≥ 12 mo since its completion
- no prior systemic treatment for LA/mBC (1L)

Stratification: non-/visceral, *ESR1* mutational status, choice of CDK4/6i, yes/no prior adjuvant CDK4/6

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Courtesy of Erika Hamilton, MD

PI3K/AKT/mTOR targeting agents for HR+/HER2- MBC

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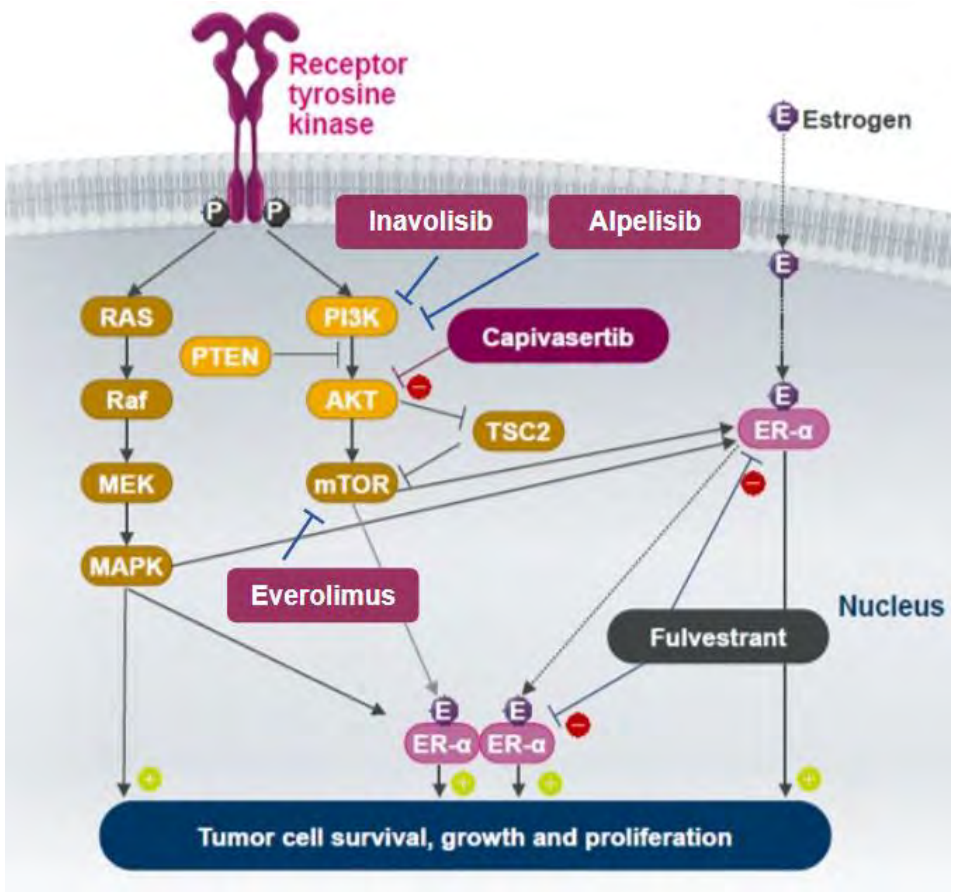
PI3K pathway often aberrantly activated in breast cancer



Breast Cancer	*PIK3CA/AKT/PTEN* alterations
HR+/HER2-	~50%
HER2+	~35-40%
TNBC	~25-30%

Everolimus – mTOR inhibitor

Alpelisib – PI3Kα inhibitor

Inavolisib – PI3Kα inhibitor

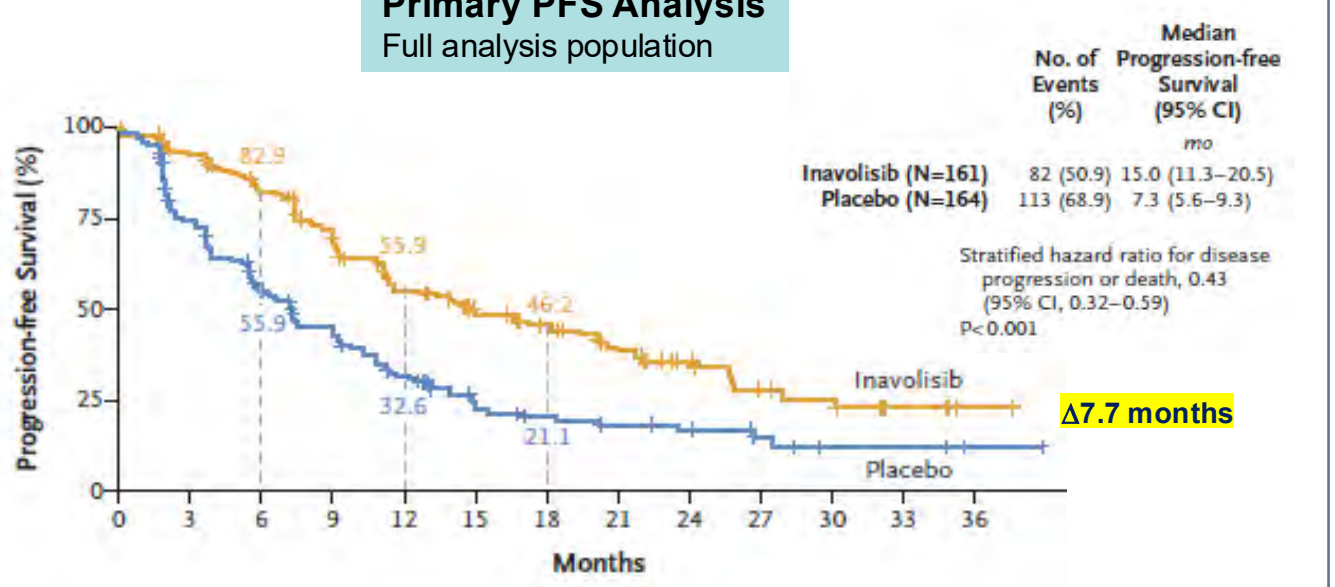
Capivasertib – AKT inhibitor

INAVO120: 1L Inavolisib/placebo + palbo + fulvestrant in PIK3CA mutant HR+/HER2- MBC

Key eligibility criteria: PIK3CA-mutated, HR+, HER2- mBC by central ctDNA or local tissue/ctDNA test, measurable disease, no prior therapy for mBC

- Progression during/within 12 mos of adjuvant ET completion, no prior therapy for mBC
- Fasting glucose <126 mg/dL and HbA1c < 6.0%

Primary PFS Analysis
Full analysis population



Patient population:

Premenopausal	38%
BMI ≥18.5 to < 25	47%
Visceral metastases	80%
Primary endocrine resistance	34%
Prior (neo)adj chemo	83%

Updated PFS Analysis
Median follow up: 34.2 months

	Events, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	103 (64.0)	17.2 (11.6–22.2)
Placebo (n = 164)	141 (86.0)	7.3 (5.9–9.2)

Stratified hazard ratio, 0.42
(95% CI = 0.32–0.55)

Statistically significant and clinically meaningful improvement in mPFS with inavolisib combination in patients with *PIK3CA* mutant HR+/HER2- MBC

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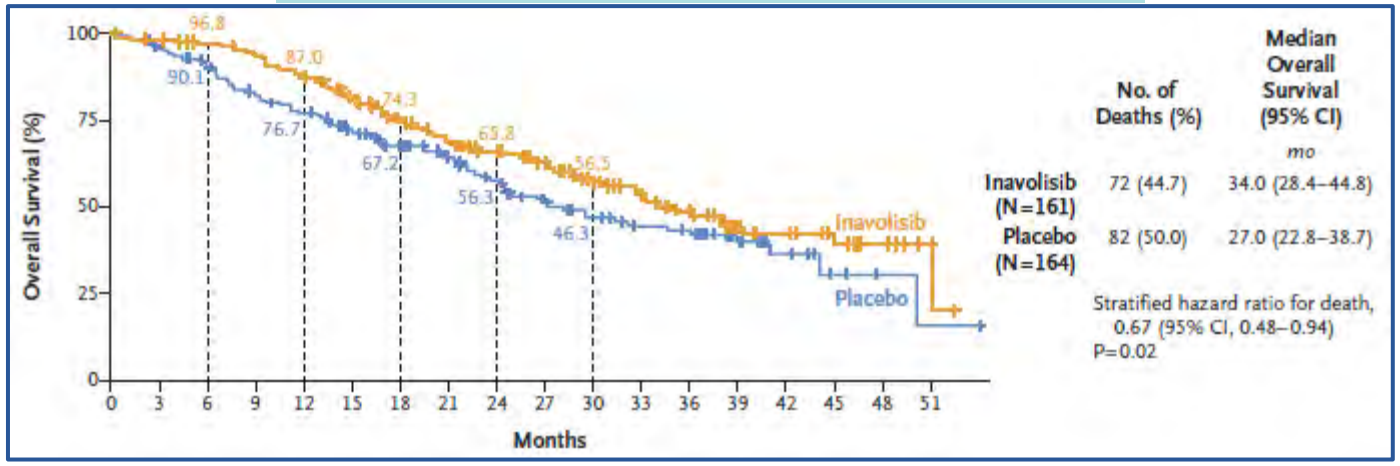
Turner NC et al. NEJM 2024; ASCO 2025

INAVO120: Overall survival and safety

Overall Survival (Median follow up: 34.2 months)
Full analysis population



Improvement in median OS: 7 months

The prespecified boundary for statistical significance ($p < 0.0469$) was crossed

Longer exposure to inavolisib did not lead to new safety signals

On October 10, 2024, the FDA approved Inavolisib in combination with palbociclib and fulvestrant for adults with *PIK3CA*-mutated HR+/HER2- MBC (1L setting)

	Inavolisib (n = 161)		Placebo (n = 163)	
Patients, n (%)	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Neutropenia	147 (91.3)	133 (82.6)	148 (90.8)	131 (80.4)
Thrombocytopenia	80 (49.7)	22 (13.7)	75 (46.0)	8 (4.9)
Stomatitis or mucosal inflammation	89 (55.3)	9 (5.6)	47 (28.8)	0
Anemia	64 (39.8)	11 (6.8)	62 (38.0)	3 (1.8)
Hyperglycemia	102 (63.4)	11 (6.8)	22 (13.5)	0
Diarrhea†	84 (52.2)	6 (3.7)	26 (16.0)	0
Nausea	47 (29.2)	0	32 (19.6)	0
Rash	43 (26.7)	0	32 (19.6)	1 (0.6)
Ocular toxicities‡	47 (29.2)	1 (0.6)	26 (16.0)	0
Aspartate transaminase/ alanine transaminase increase	34 (21.1)	7 (4.3)	37 (22.7)	4 (2.5)
Vomiting	26 (16.1)	2 (1.2)	10 (6.1)	2 (1.2)
Lymphopenia	6 (3.7)	1 (0.6)	15 (9.2)	3 (1.8)
Pneumonitis§	5 (3.1)	1 (0.6)	2 (1.2)	0

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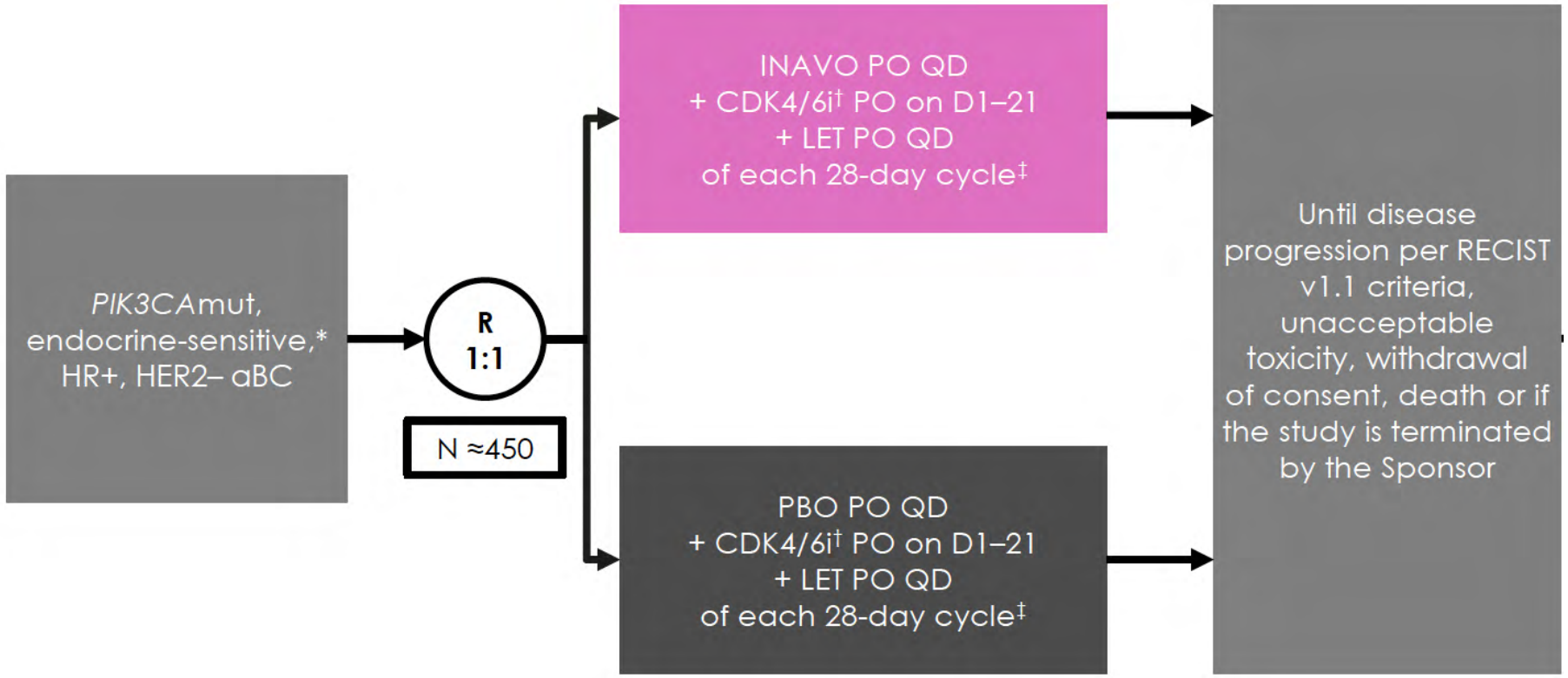
Jhaveri et al. NEJM 2025; Turner NC et al. ASCO 2025

INAVO123: 1L Inavolisib/placebo + CDK4/6i + letrozole for *PIK3CA*m endocrine sensitive HR+/HER2- MBC

Trial is currently enrolling



Endocrine sensitive: *De novo* or relapsed after at least 2 years of standard neoadjuvant/adjuvant endocrine therapy

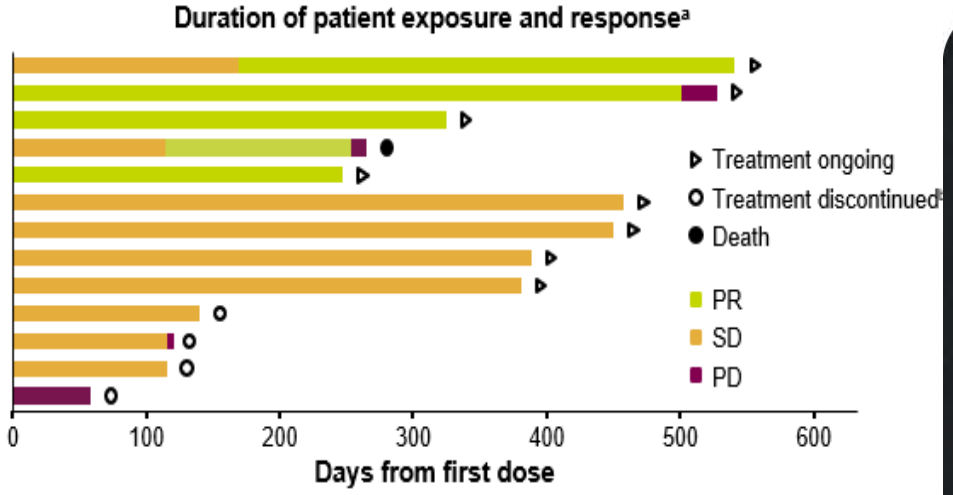
Cortes J et al. ESMO Breast 2025; Abstract 408TiP.

CAPItello-292: Trial with Capivasertib + CDK4/6i + fulvestrant for HR+/HER2- MBC

Rationale: Simultaneously inhibiting PI3K/AKT and CDK4/6 pathways may delay CDK4/6i resistance
Capivasertib is selective inhibitor of all three isoforms of AKT

The trial is a phase1b/3 study; ph1b is the dose finding phase to determine the optimal dose of capivasertib to use in combination with CDK4/6i+ ET

Ph1b: Activity with Capivasertib(400mg)+ palbo+fulvestrant



Key Eligibility:

- Locally advanced or mBC
- Relapsed on or within 12 months of completing adjuvant ET (tam, AI or SERD)
- Maximum 1 line of chemo in advanced setting
- No prior PI3K/AKT/mTORi
- **No prior CDK4/6i in the metastatic setting** (CDK4/6i adjuvant allowed with a disease free interval of at least 12 months from completion)
- **No prior ET in the metastatic setting**

Stratification Factors:

- Liver metastases (Y/N)
- Sensitivity to prior hormonal therapy (Y/N)
- Investigator's choice of CDK (Palbo/Ribo)

Study to start with **palbociclib only, with ribociclib added after RP3D** determined from Ph1b

CAPItello-292 Randomized Phase 3

1:1 R N=628

- B: fulvestrant + CDK4/6 (initially palbociclib only available CDK4/6)
  - Additional CDK4/6 available (ribociclib)
- A: capivasertib+fulvestrant+CDK4/6 (initially palbociclib only available CDK4/6)
  - Additional CDK4/6 RP3D available (ribociclib)

- Treatment until disease progression by BICR, unacceptable toxicity, patient withdrawal

Endpoints

Primary: PFS by BICR in overall population

Key Secondary: OS overall, ORR

Secondary: PFS in altered subgroup, PFS2, Safety, ctDNA clearance (exploratory)

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Hamilton E et al. SABCS 2023; Neven P et al. ESMO 2025

Summary

- 1L CDK4/6i +ET is superior to chemotherapy even in patients with high tumor burden (RIGHT Choice, ABIGAIL, AMBRE)
- Oral SERDs in combination + CDK4/6i are under investigation in 1L HR+/HER2- MBC with the goal of replacing AI as the ET backbone (SERENA-4, pionERA)
- ctDNA guided switching of therapy to camizestrant at emergence of *ESR1* mutations prolonged 1st line PFS (SERENA-6) but clinical utility remains to be demonstrated
- Endocrine resistance due to PI3K/AKT/mTOR pathway activation can be overcome by using targeted agents like capivasertib and inavolisib (INAVO120)
- Although efficacious, the current approved PI3K inhibitors do not have a favorable side effect profile
  - Opportunity: Development of novel agents with improved side effect profile
- Optimal therapy for treatment of 1L HR+/HER2- MBC depends on endocrine sensitivity of the tumor as well as the mutational profile

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Treatment algorithm for HR+/HER2- MBC

1L therapy

- AI + CDK4/6i
- Early relapse on adjuvant AI: Fulvestrant + CDK4/6i
- Early Relapse AND PIK3CA mutation: Fulvestrant + palbociclib + inavolisib

2L therapy

- No mutation: Fulv + Abema; Exe + evero; Abemaciclib
- PI3K family mut: Fulv+ alpelisib; Fulv + capi
- ESR1 mutation: Elacestrant; Imlunestrant
- ESR1 mutation: Elacestrant; Imlunestrant

When endocrine resistant:

3L+ therapy

- T-DXd/ Sacituzumab govitecan/ Dato-DXd/ or chemotherapy

QUESTIONS?

Module 10: HR-Positive Breast Cancer

Current and Future Management of HR-Positive, HER2-Negative Localized Breast Cancer — Dr Meisel

Optimizing First-Line Therapy for Patients with HR-Positive mBC — Dr Hamilton

Current and Future Role of Oral SERDs for Progressive HR-Positive mBC — Dr Wander

Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr O'Shaughnessy

Mass General Brigham
Mass General Cancer Center

Current and Future Role of Oral SERDs for Progressive HR-Positive Metastatic Breast Cancer

Research To Practice: Fifth Annual National General Medical Oncology Summit
Orlando, FL
April 26th, 2026

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Disclosures

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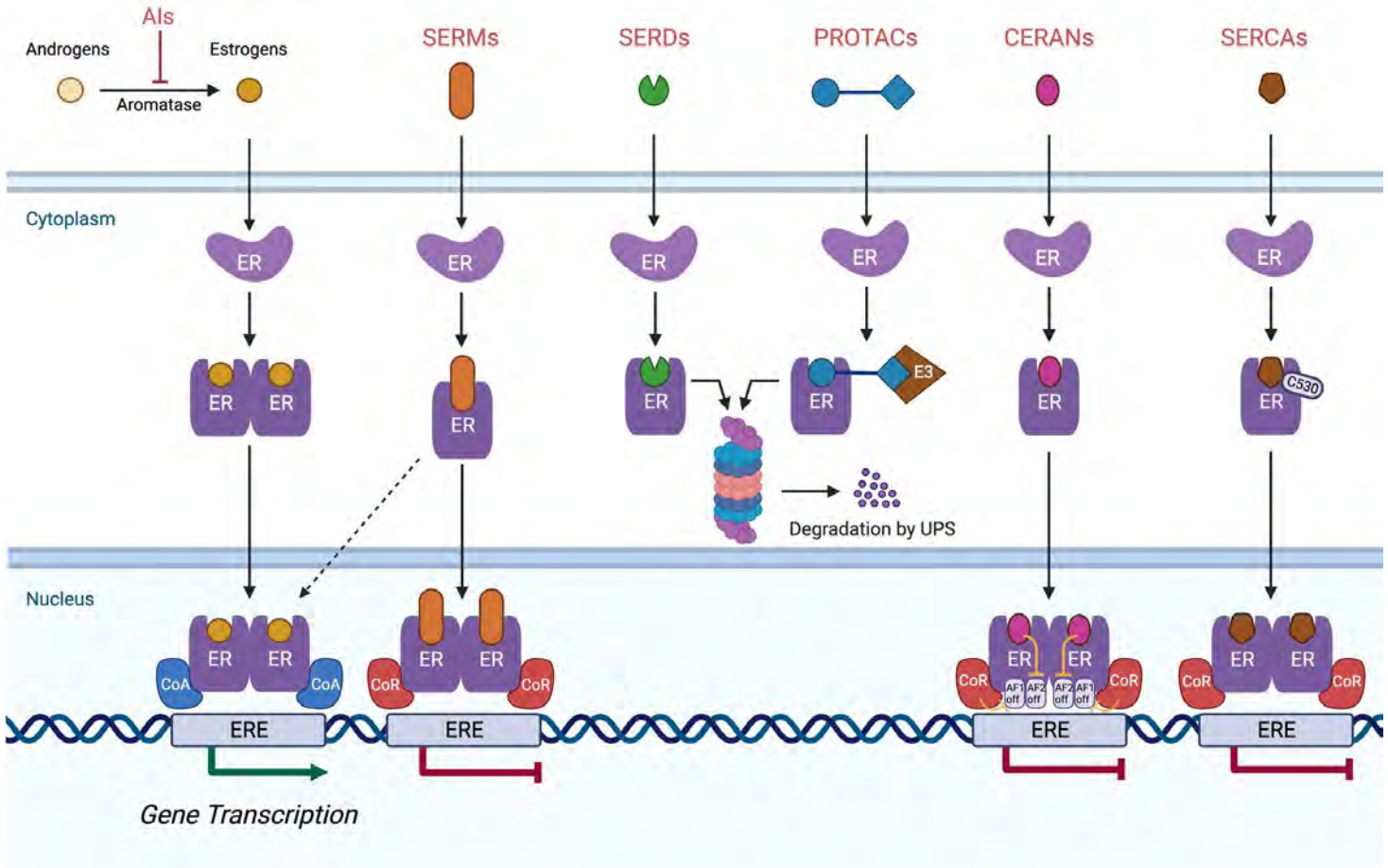
Contracted Research	Arvinas, Genentech, a member of the Roche Group, Lilly, Menarini Group, Nuvation Bio Inc, Pfizer Inc, Phoenix Molecular Designs, Puma Biotechnology Inc, Regor Therapeutics, Sermonix Pharmaceuticals, Stemline Therapeutics Inc

Oral SERDs for HR+/HER2- Metastatic Breast Cancer

- Elacestrant monotherapy in endocrine-refractory disease (**EMERALD**)
- Imlunestrant alone and with abemaciclib (**EMBER3**)
- Giredestrant and everolimus for CDK4/6i-resistant disease (**evERA**)
- Emerging oral SERD combination regimens and key trials
- Summary, key questions, future directions

Emerging Antiestrogen Agents with Novel Mechanisms



AI: Aromatase Inhibitor

SERM: Selective ER Modulator

SERD: Selective ER Degrader

PROTAC: Proteolysis Targeting Chimeric

CERAN: Complete ER Antagonist

SERCA: Selective ER Covalent Antagonist

Patel R et al NPJ Breast Cancer 2023

Oral SERDs for HR+/HER2- Metastatic Breast Cancer

- Elacestrant monotherapy in endocrine-refractory disease (**EMERALD**)
- Imlunestrant alone and with abemaciclib (**EMBER3**)
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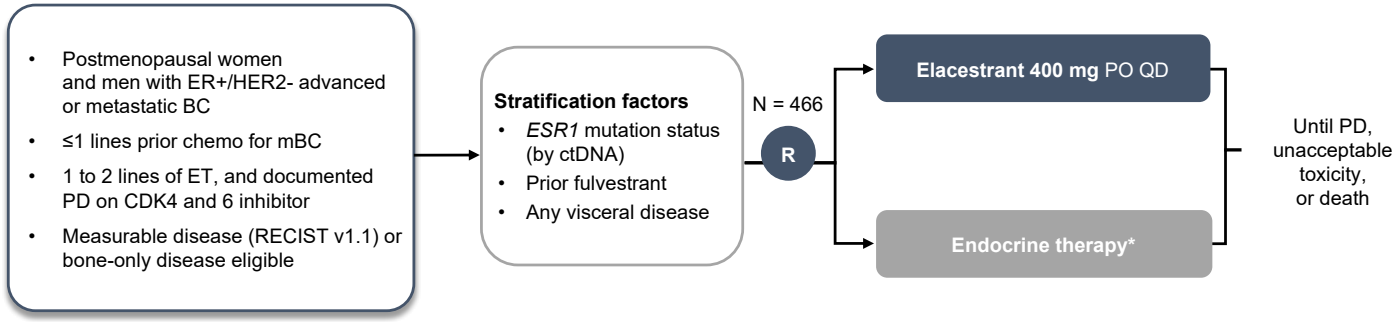
EMERALD: Elacestrant Phase III

Patient Characteristics: Elacestrant vs. Control

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

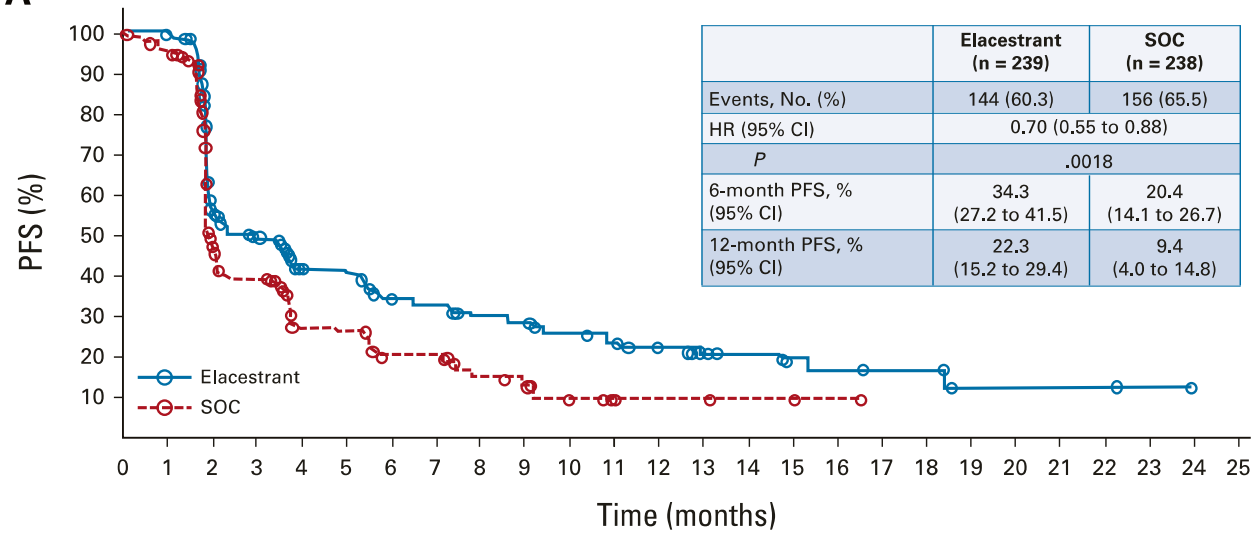


Median PFS Improvements:

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

A

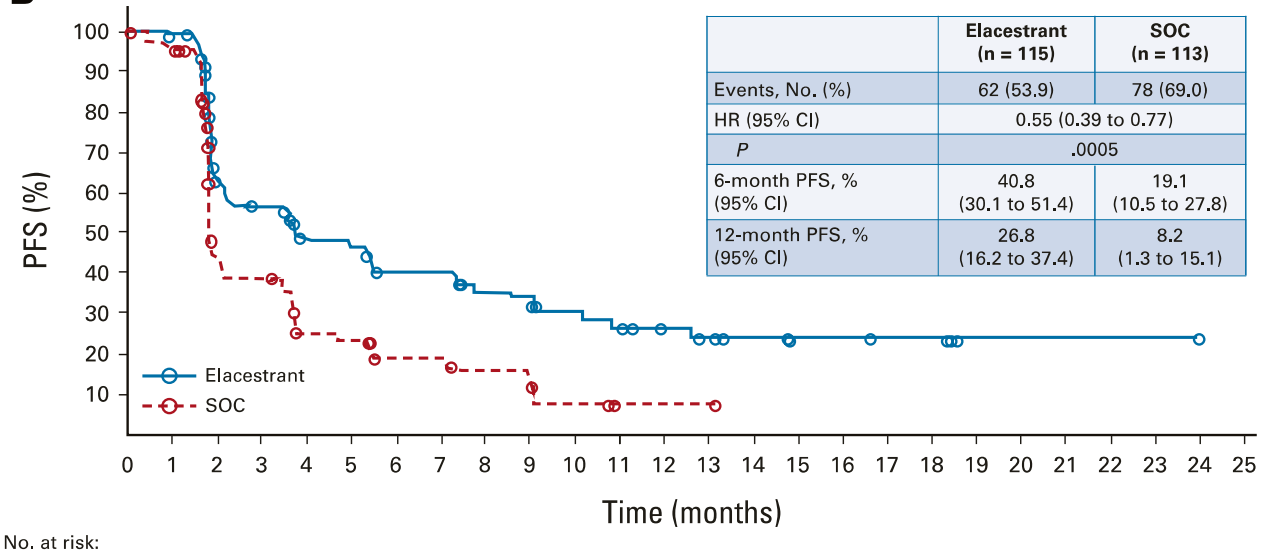


	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

No. at risk:

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

B



	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)

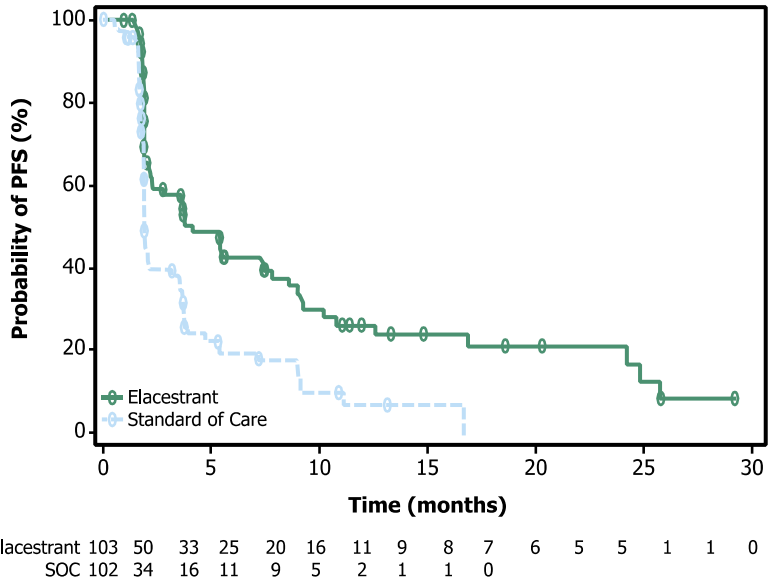
No. at risk:

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Bidard FC et al JCO 2022

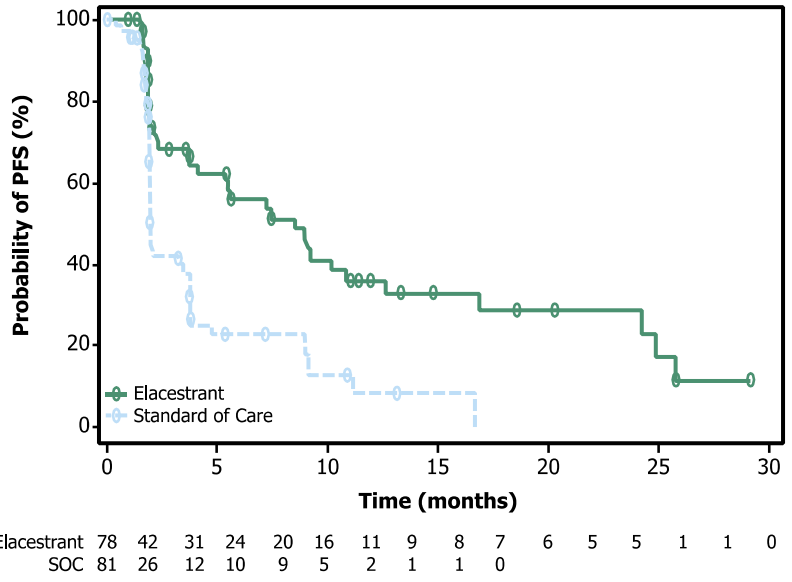
EMERALD: Efficacy Subgroups

At least 6 mo CDK4/6i



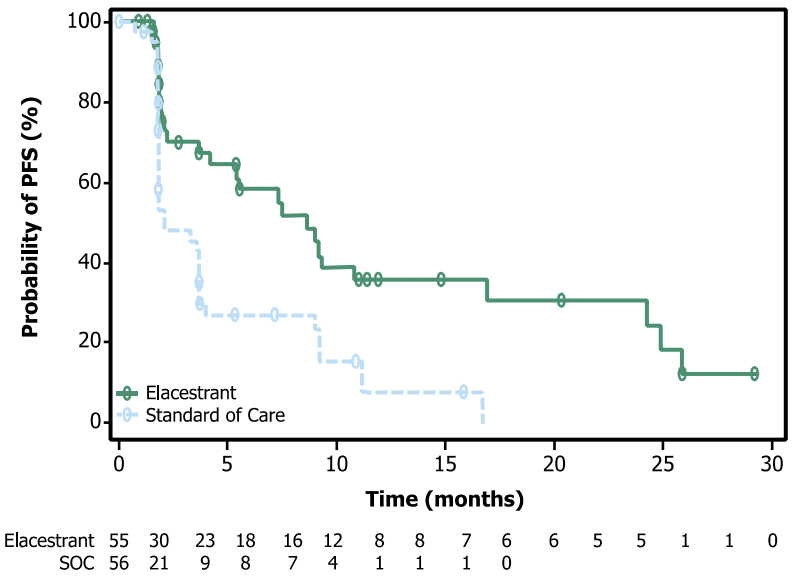
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



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

At least 18 mo CDK4/6i



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

Bardia et al CCR 2024; Kaklamani et al. ASCO 2023

EMERALD: Elacestrant Toxicity Experience

AEs[c] Occurring in ≥ 10% of Patients in Any Arm	Elacestrant		Total		Fulvestrant		AI	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	0	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0	12 (7.5)	0	7 (10.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	0	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0	28 (17.4)	0	9 (13.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	0
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	0
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0	18 (11.2)	0	8 (11.8)	0
Constipation	29 (12.2)	0	15 (6.6)	0	10 (6.2)	0	5 (7.4)	0
Hot flush	27 (11.4)	0	19 (8.3)	0	15 (9.3)	0	4 (5.9)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0	4 (2.5)	0	2 (2.9)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	0	6 (8.8)	1 (1.5)

Elacestrant Monotherapy:
Dose Reduction Rate: 3%
Discontinuation Rate: 6.3%

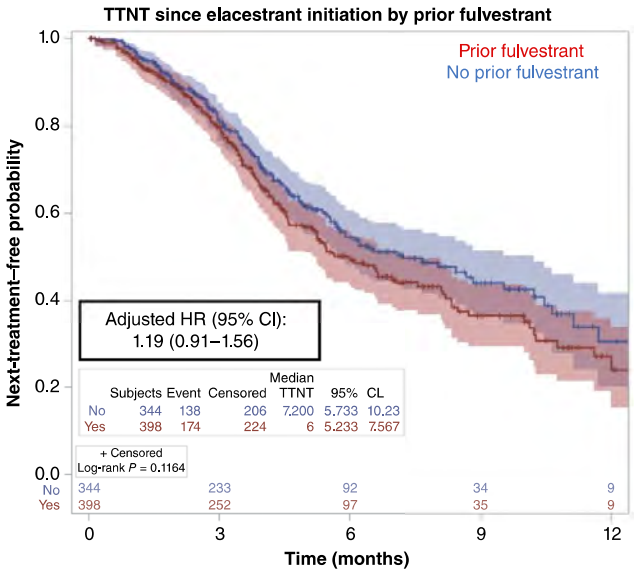
Bidard FC et al JCO 2022

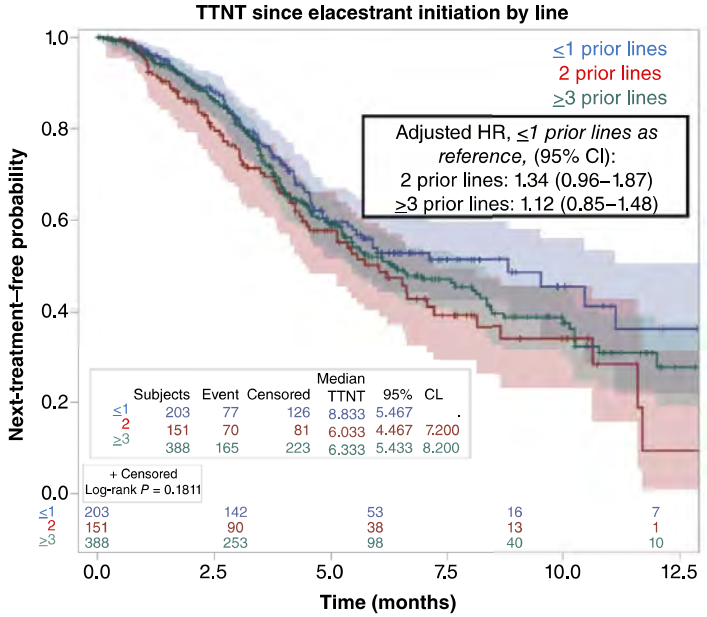
Elacestrant Real-World Data

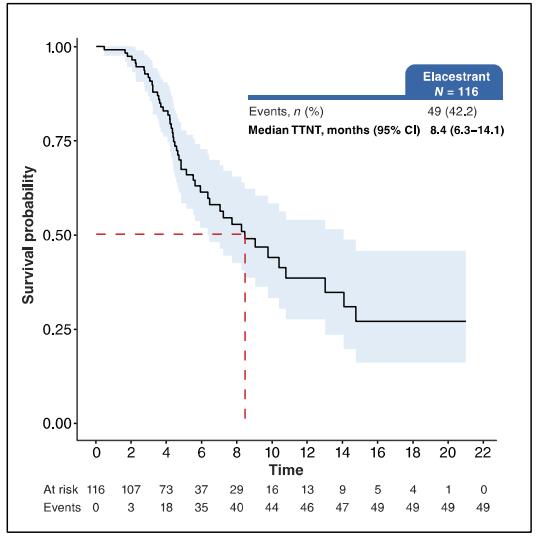
Retrospective claims-based clinico-genomic database analyses

Lloyd et al
GuardantINFORM
n=742
52% prior fulvestrant
38% prior chemotherapy
75% visceral disease

Rugo et al
Komodo/FMI
n=306
72% prior fulvestrant
50% prior chemotherapy
87% visceral disease
94% 1L CDKi >12m







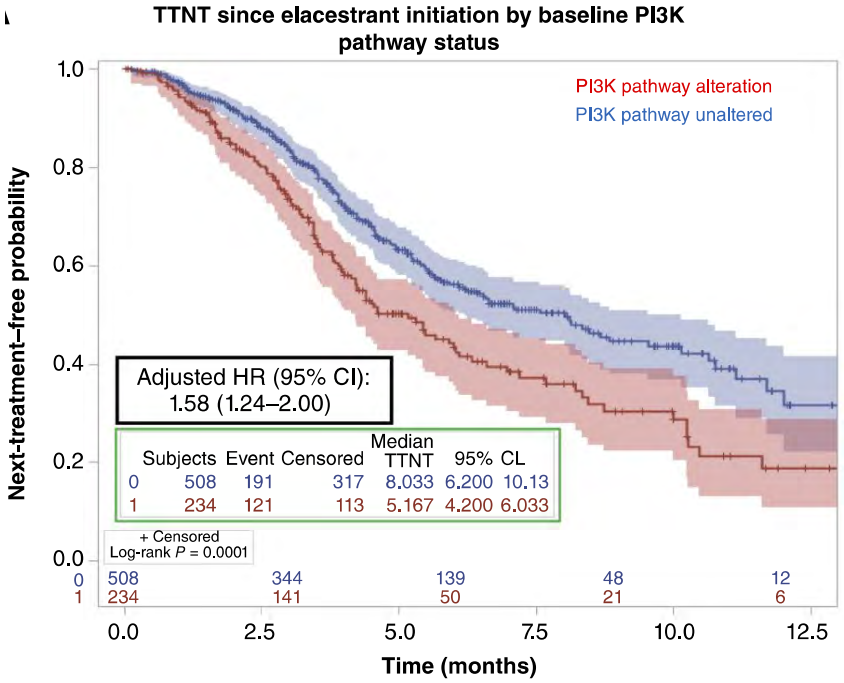
Median TTNT 6-9 months

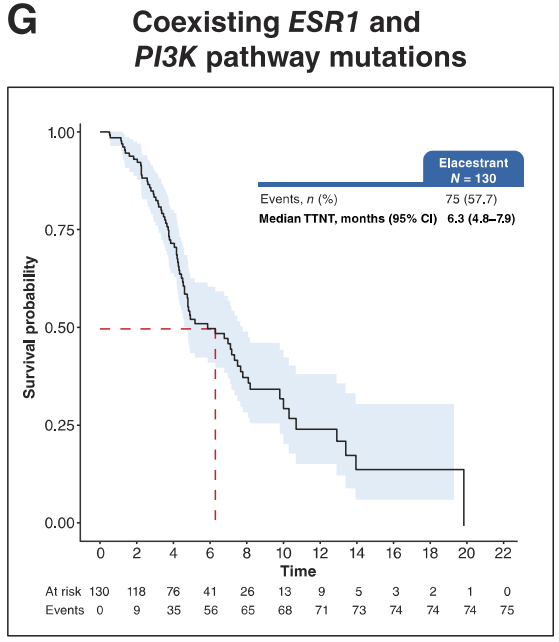
- Trend toward longer TTNT
  - with less prior therapy (eg @2L)
  - without prior fulvestrant
- No impact with visceral metastatic disease

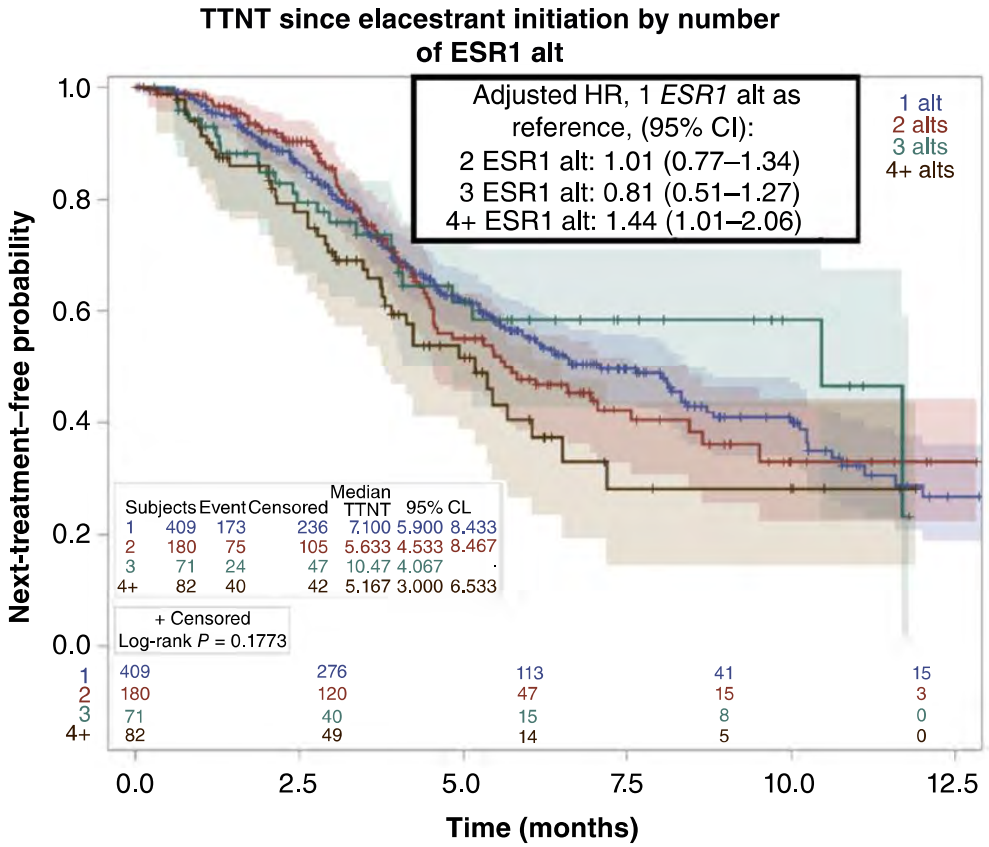
Lloyd MR et al CCR 2026; Rugo H et al CCR 2026

Elacestrant Real-World Data

- Concurrent ESR1/PIK3CA altercations with reduced TTNT
- Equally efficacious with ESR1 Y537S vs other alterations
- Trend toward inferior outcomes with higher degree of polyclonality (4+ alterations)







Lloyd MR et al CCR 2026; Rugo H et al CCR 2025

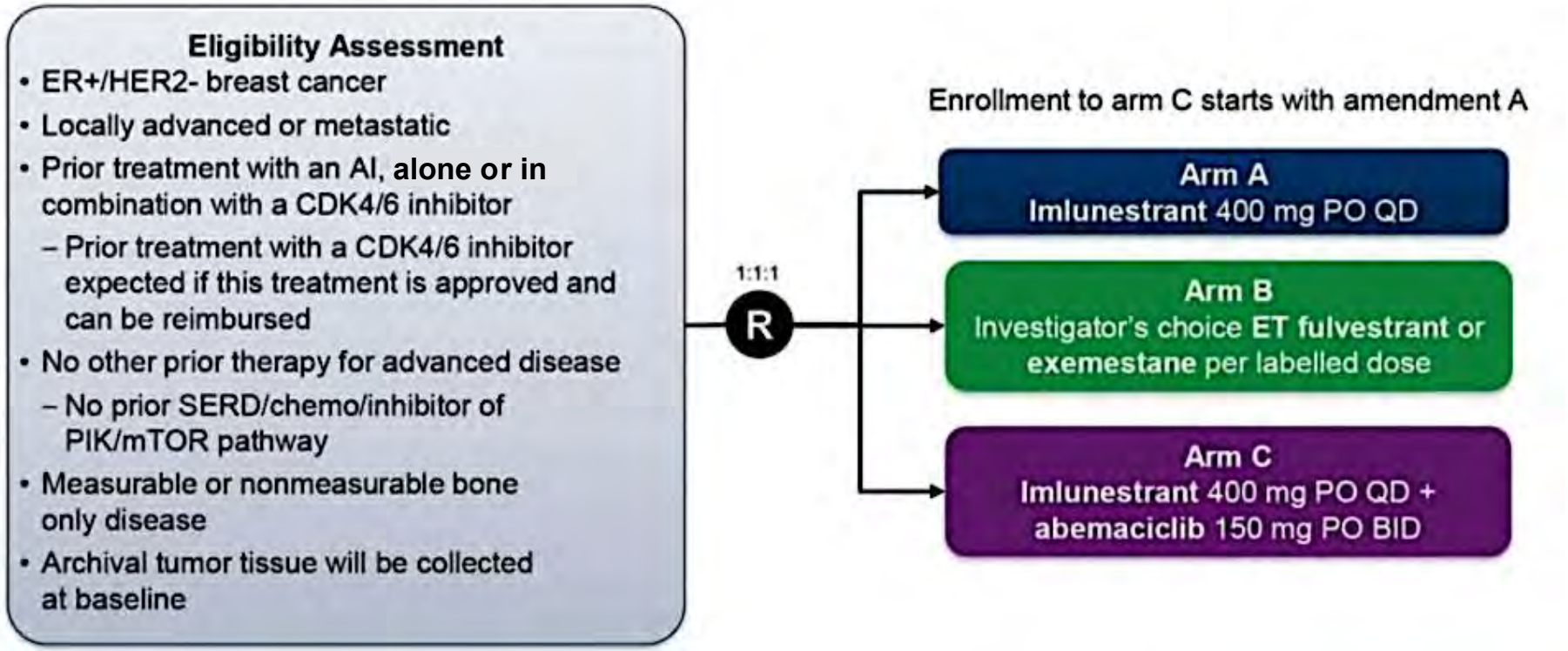
Oral SERDs for HR+/HER2- Metastatic Breast Cancer

- Elacestrant monotherapy in endocrine-refractory disease (**EMERALD**)
- Imlunestrant alone and with abemaciclib (**EMBER3**)
- Giredestrant and everolimus for CDK4/6i-resistant disease (**evERA**)
- Emerging oral SERD combination regimens and key trials
- Summary, key questions, future directions

EMBER3: Imlunestrant Phase III

Patient Characteristics: Imlunestrant vs. Control

- No prior chemotherapy, 1 prior line of ET
- ~40% of patients were CDK4/6i-naive
- ESR1m: 41.7% vs 35.8



Jhaveri KL et al NEJM 2024

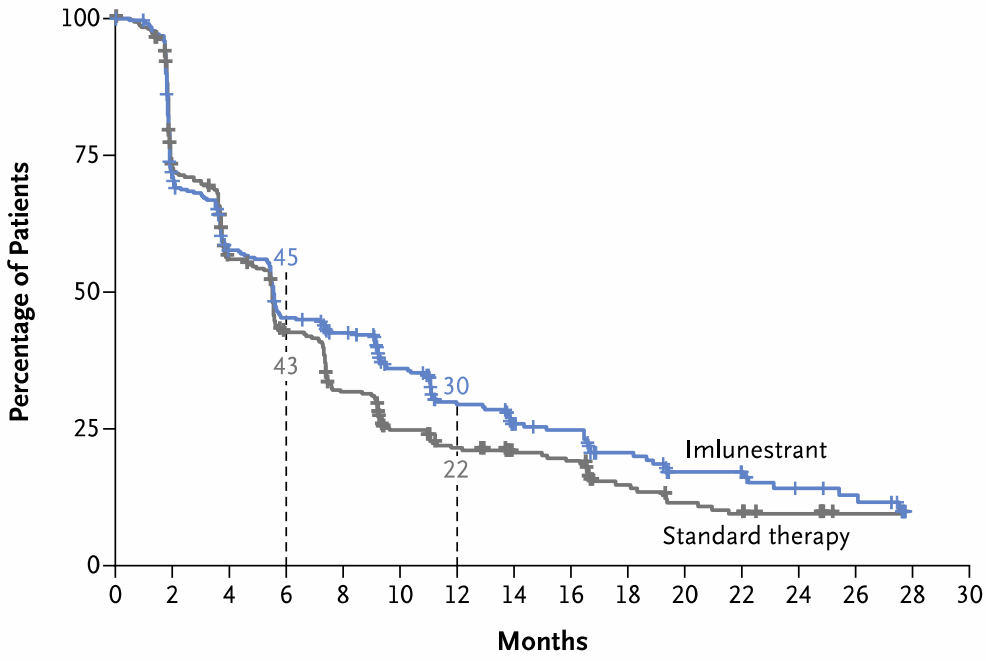
EMBER3: Imlunestrant Phase III

Median PFS Improvements:

ITT: 5.5 > 5.6m; HR (95%CI) 0.87 (0.72-1.04), p=0.12

ESR1m: 3.8 > 5.5m; Restricted mean survival diff (95%CI) 2.6m (1.2-3.9), p<0.001

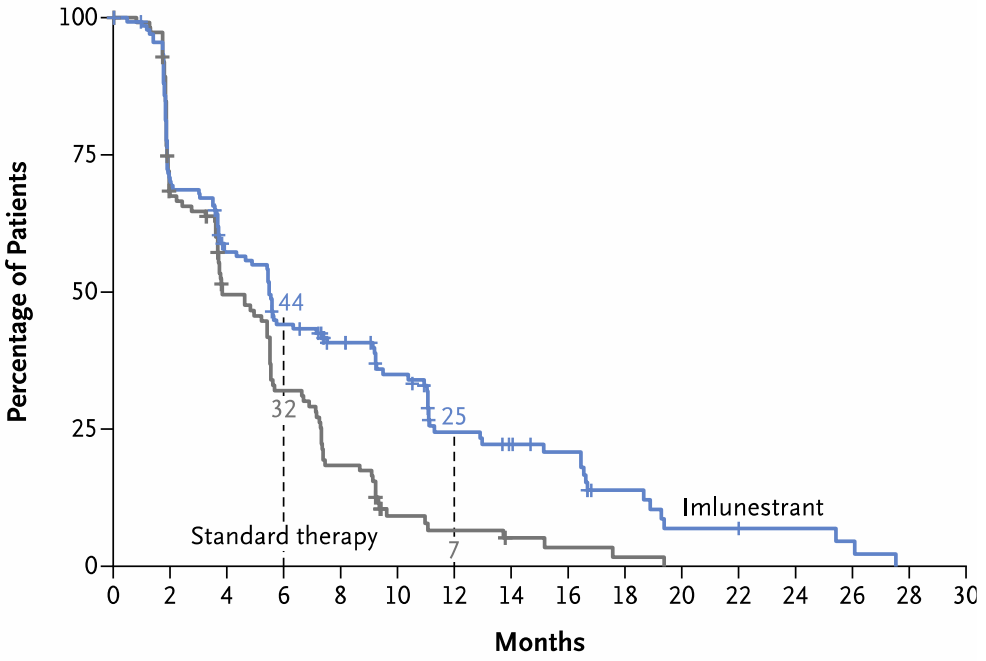
B **Progression-free Survival among All Patients, Imlunestrant vs. Standard Therapy**



No. at Risk

Imlunestrant	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0
Standard therapy	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

A **Progression-free Survival among Patients with *ESR1* Mutations, Imlunestrant vs. Standard**



No. at Risk

Imlunestrant	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0
Standard therapy	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

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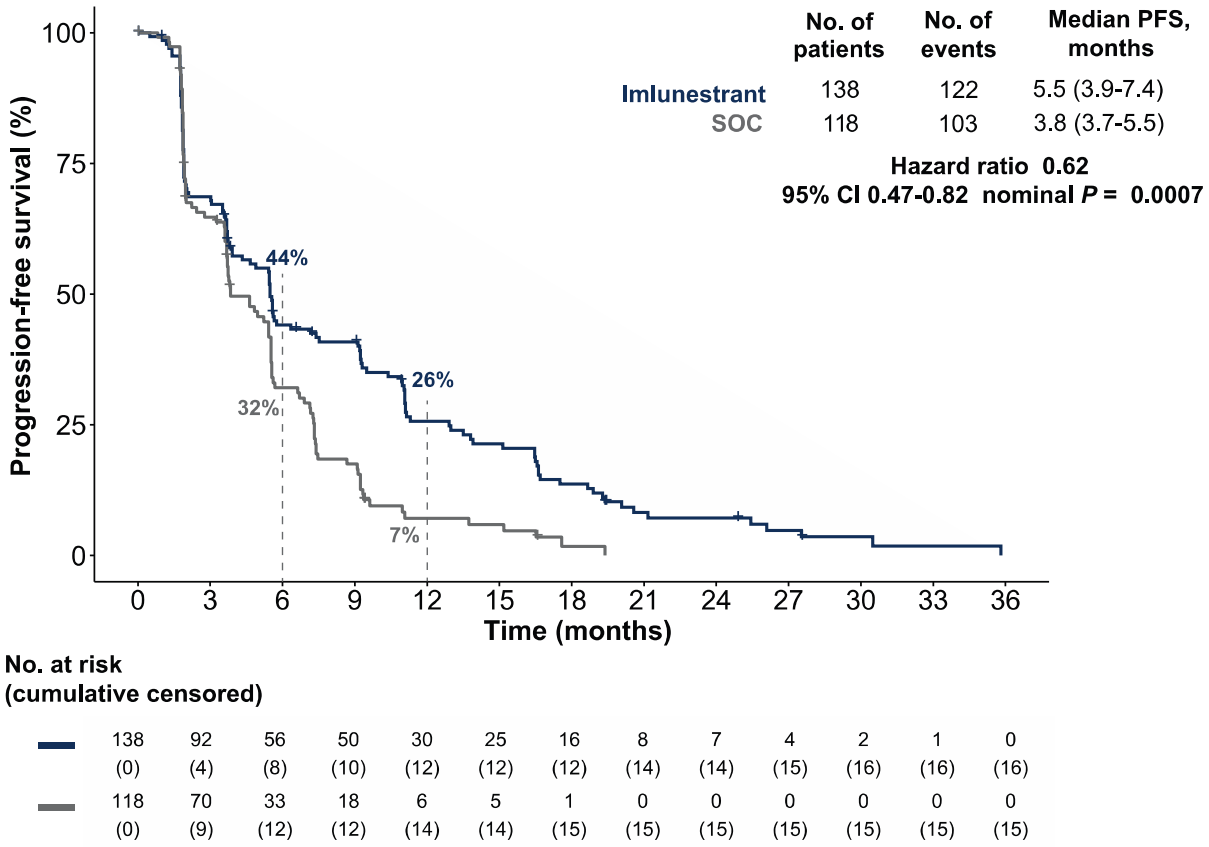
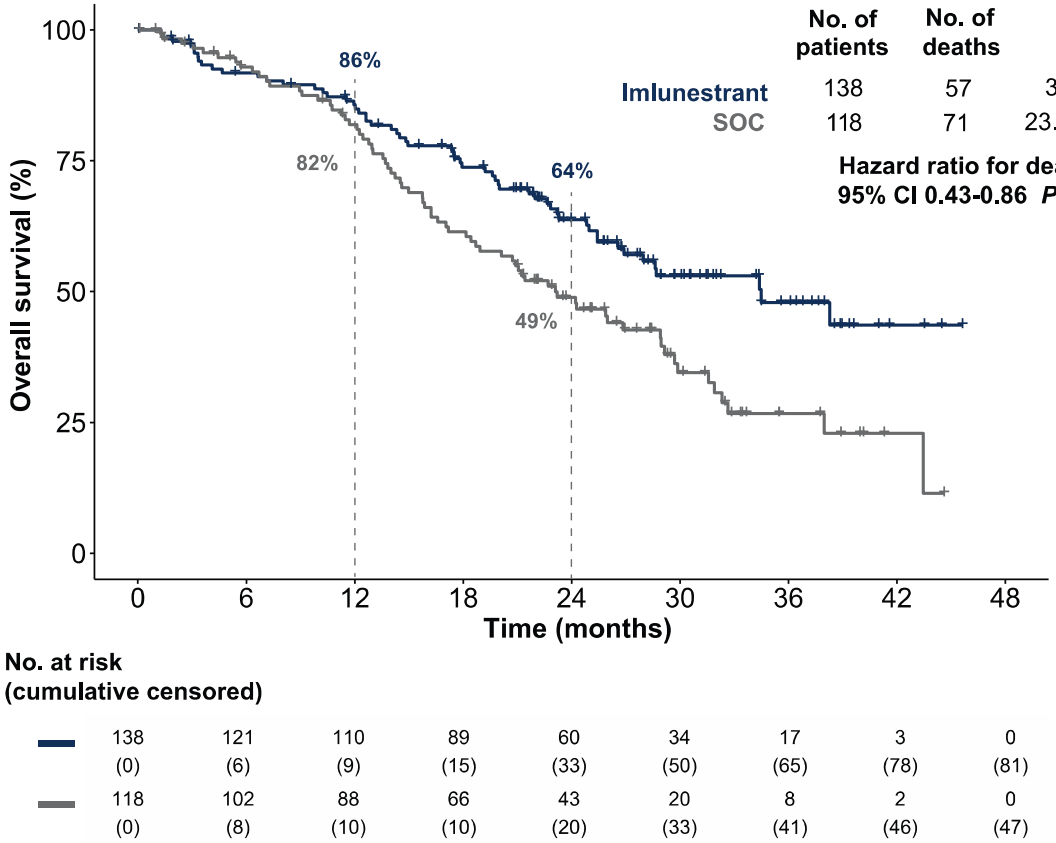
EMBER3: Updated ESR1m Single Agent Efficacy



	No. of patients	No. of events	Median PFS, months
Imlunestrant	138	122	5.5 (3.9-7.4)
SOC	118	103	3.8 (3.7-5.5)

Hazard ratio 0.62
95% CI 0.47-0.82 nominal *P* = 0.0007

Median PFS Improvements:
ESR1m PFS: 3.8 > 5.5m; HR (95%CI) 0.62 (0.47-0.82), p=0.0007
ESR1m OS: 23.1 > 34.5m; HR (95%CI) 0.60 (0.43-0.86), p=0.0043
(not yet at target significance)



	No. of patients	No. of deaths	Median OS, months
Imlunestrant	138	57	34.5 (25.4-NR)
SOC	118	71	23.1 (18.4-28.9)

Hazard ratio for death 0.60
95% CI 0.43-0.86 *P* = 0.0043

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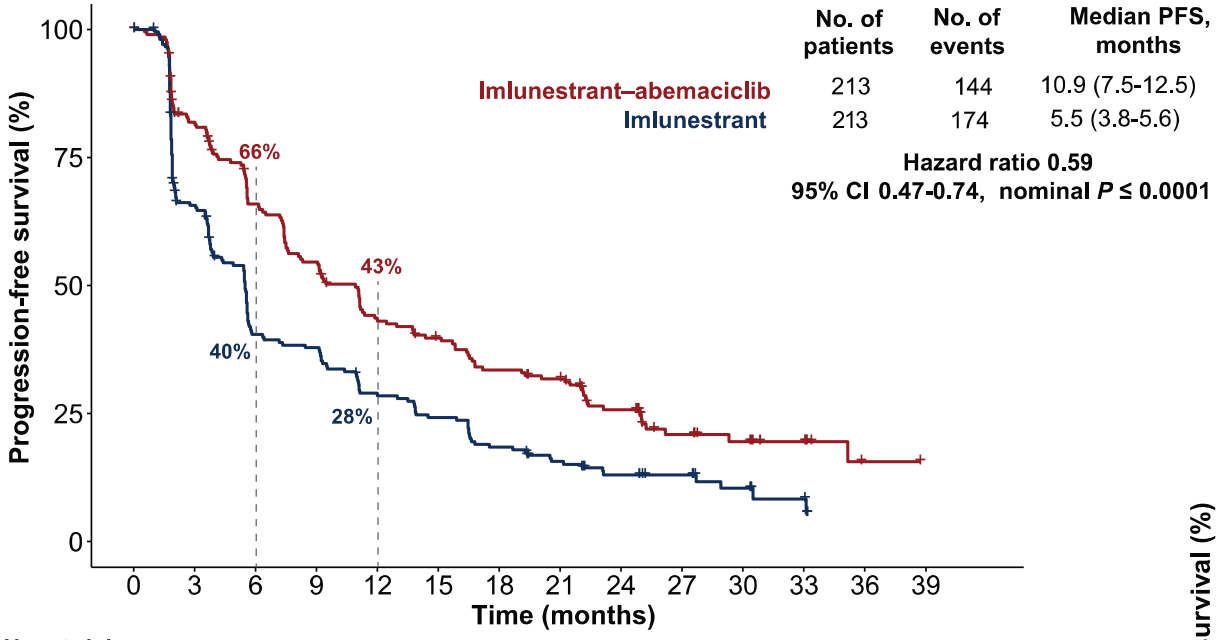
EMBER3: (Updated) Imlunestrant + Abemaciclib Efficacy



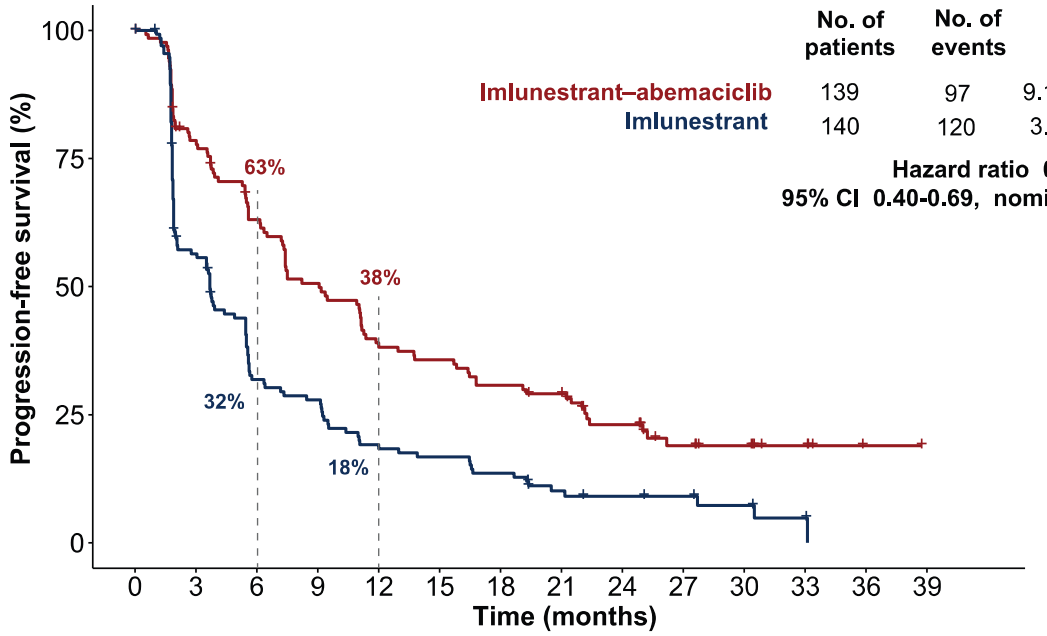
	No. of patients	No. of events	Median PFS, months
Imlunestrant–abemaciclib	213	144	10.9 (7.5-12.5)
Imlunestrant	213	174	5.5 (3.8-5.6)

Hazard ratio 0.59
95% CI 0.47-0.74, nominal $P \leq 0.0001$

No. at risk
(cumulative censored)

	213	159	122	101	78	70	59	54	36	20	14	10	2	0
	(0)	(18)	(25)	(25)	(27)	(29)	(29)	(31)	(40)	(51)	(56)	(60)	(67)	(69)
	213	130	78	73	54	46	35	26	18	14	8	4	0	0
	(0)	(13)	(16)	(16)	(17)	(17)	(17)	(21)	(25)	(29)	(33)	(36)	(39)	(39)

Median PFS for Imlunestrant/Abema:
ITT: 10.9m (95% CI 7.5-12.5)
Post CDK4/6i: 9.1m (95% CI 7.2-11.3)



	No. of patients	No. of events	Median PFS, months
Imlunestrant–abemaciclib	139	97	9.1 (7.2-11.3)
Imlunestrant	140	120	3.7 (2.1-5.5)

Hazard ratio 0.53
95% CI 0.40-0.69, nominal $P \leq 0.0001$

No. at risk
(cumulative censored)

	139	100	76	61	46	43	37	34	21	13	9	5	1	0
	(0)	(11)	(16)	(16)	(16)	(16)	(16)	(17)	(24)	(29)	(33)	(37)	(41)	(42)
	140	73	40	35	23	21	17	10	7	6	4	2	0	0
	(0)	(9)	(11)	(11)	(11)	(11)	(11)	(14)	(16)	(17)	(18)	(19)	(20)	(20)

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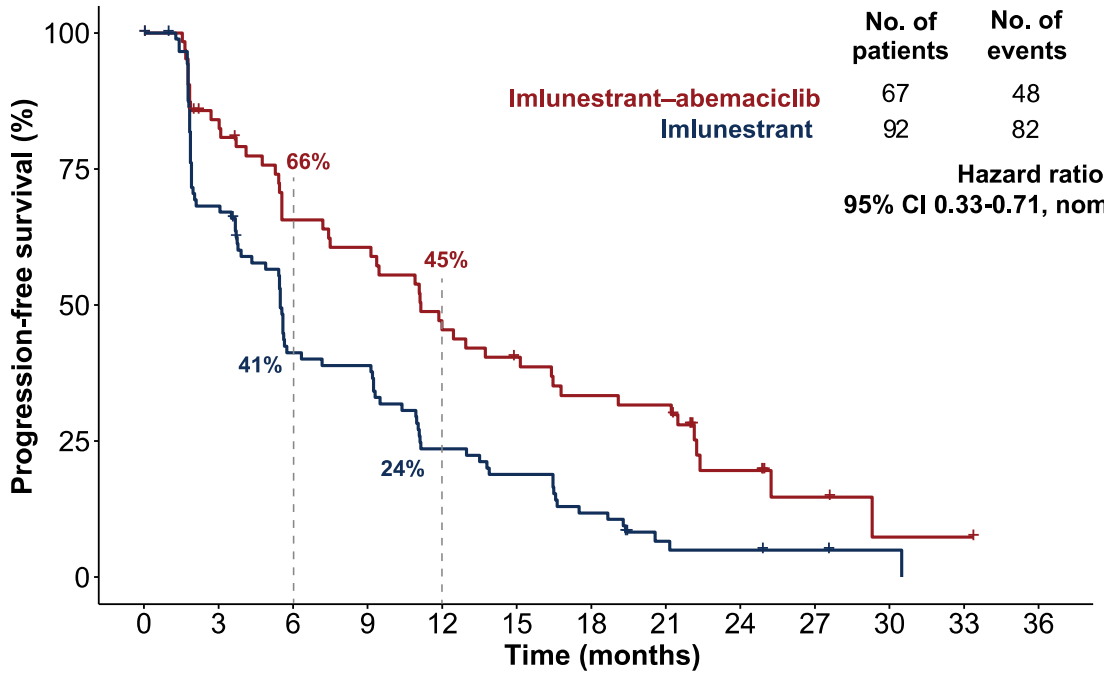
EMBER3: Imlunestrant + Abemaciclib Efficacy (by ESR1 Status)



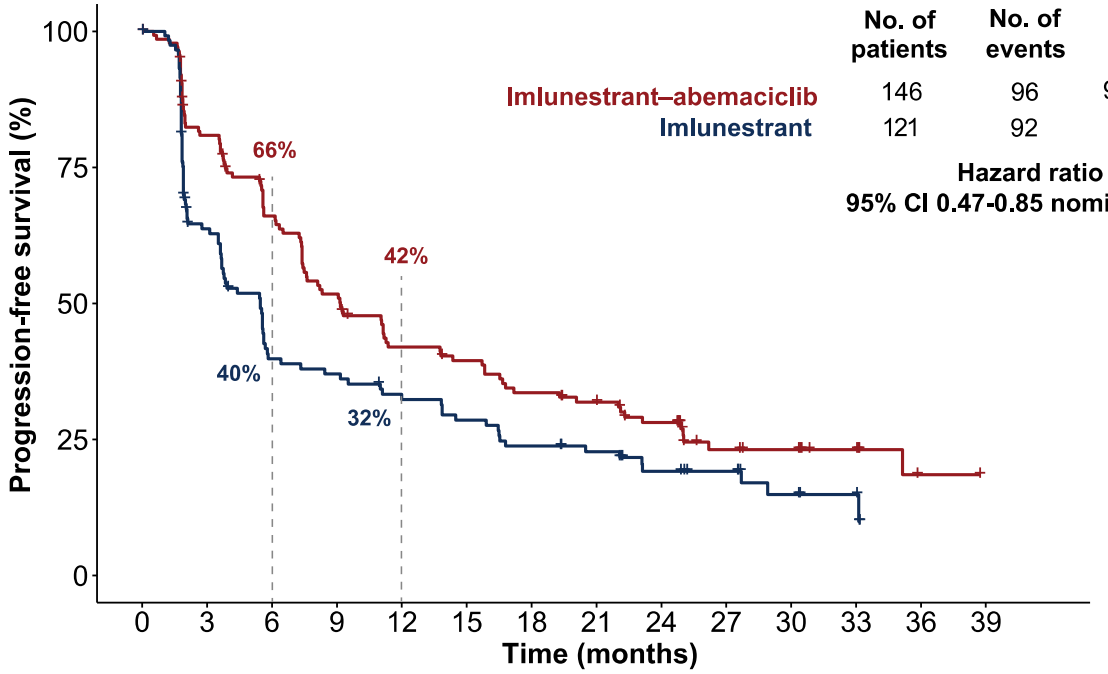
	No. of patients	No. of events	Median PFS, months
Imlunestrant–abemaciclib	67	48	11.1 (7.4-16.4)
Imlunestrant	92	82	5.5 (3.8-7.2)

Hazard ratio 0.49
95% CI 0.33-0.71, nominal *P* = 0.0002

No. at risk
(cumulative censored)

	67	51	39	36	27	23	19	18	7	3	1	1	0
	(0)	(6)	(7)	(7)	(7)	(8)	(8)	(8)	(14)	(17)	(18)	(18)	(19)
	92	60	35	33	20	16	10	4	3	2	1	0	0
	(0)	(4)	(6)	(6)	(6)	(6)	(6)	(8)	(8)	(9)	(10)	(10)	(10)

Median PFS for Imlunestrant/Abema:
ESR1m: 11.1m (95% CI 7.4-16.4)
ESR1wt: 9.2m (95% CI 7.4-13.8)



	No. of patients	No. of events	Median PFS, months
Imlunestrant–abemaciclib	146	96	9.2 (7.4-13.8)
Imlunestrant	121	92	5.5 (3.6-5.8)

Hazard ratio 0.64
95% CI 0.47-0.85 nominal *P* = 0.0023

No. at risk
(cumulative censored)

	146	108	83	65	51	47	40	36	29	17	13	9	2	0
	(0)	(12)	(18)	(18)	(20)	(21)	(21)	(23)	(26)	(34)	(38)	(42)	(48)	(50)
	121	70	43	40	34	30	25	22	15	12	7	4	0	0
	(0)	(9)	(10)	(10)	(11)	(11)	(11)	(13)	(17)	(20)	(23)	(26)	(29)	(29)

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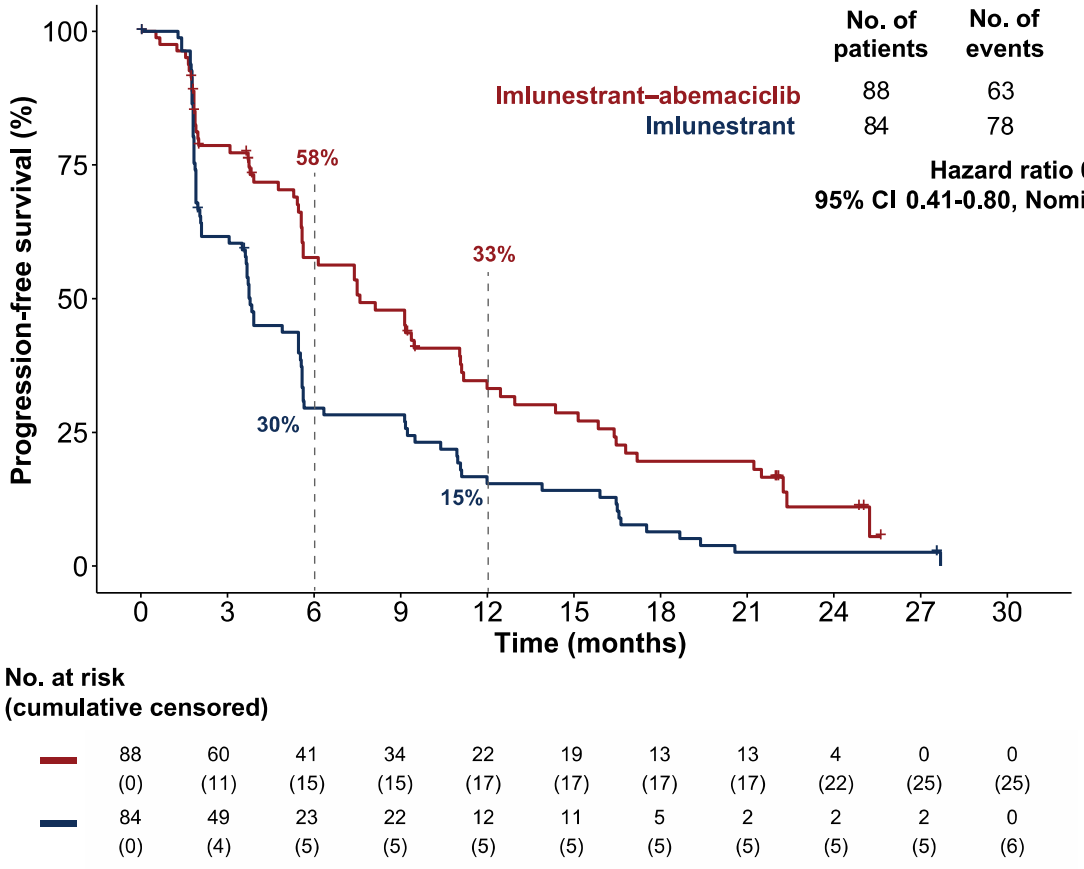
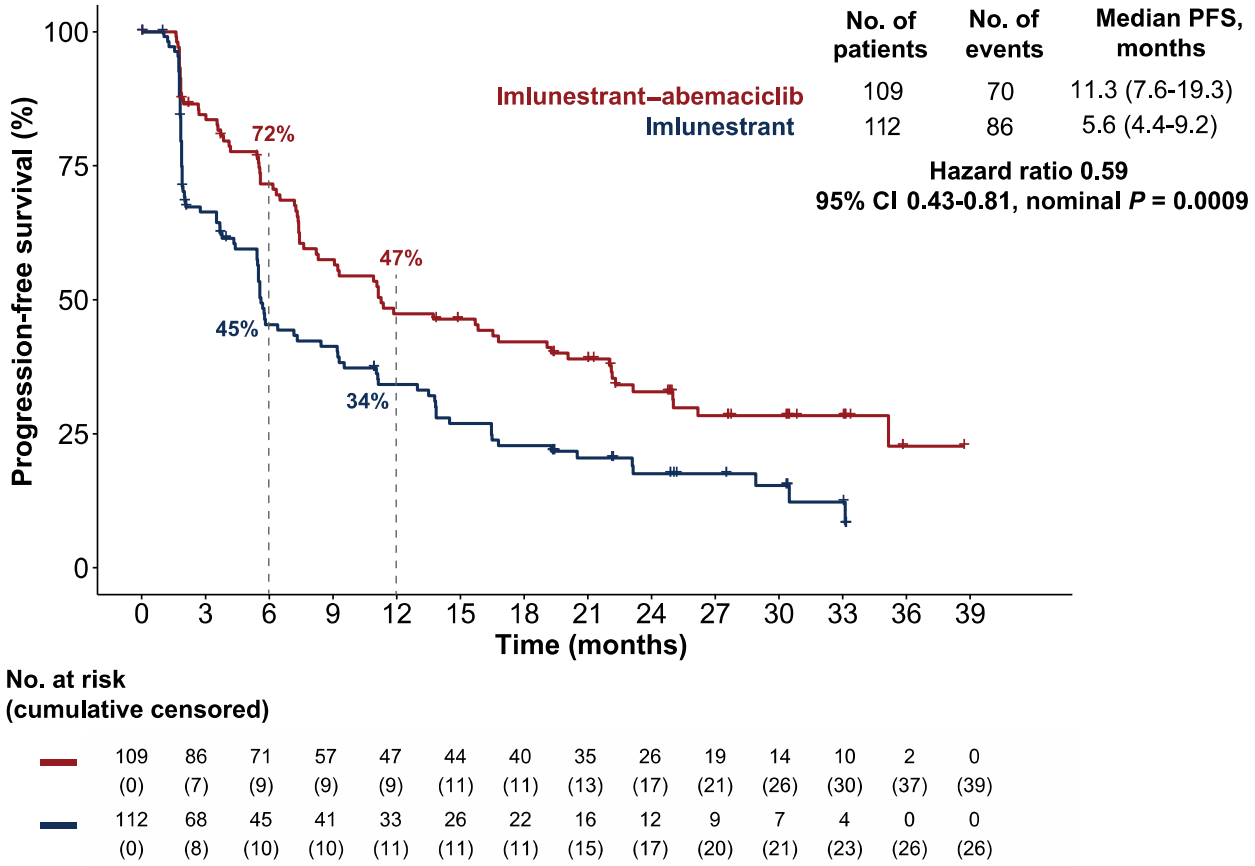
EMBER3: Imlunestrant + Abemaciclib Efficacy (by PI3K Status)



Median PFS for Imlunestrant/Abema:

PIK3CAm: 7.6m (95% CI 5.6-11.1)

PIK3CAwt: 11.3m (95% CI 7.6-19.3)



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EMBER3: Imlunestrant +/- Abemaciclib Toxicity

Table 2. Adverse Events According to Grade (Safety Population).*

Event	Imlunestrant (N=327)		Standard Therapy (N=324)		Imlunestrant–Abemaciclib (N=208)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)					
Any adverse event	270 (82.6)	56 (17.1)	273 (84.3)	67 (20.7)	204 (98.1)	101 (48.6)
Fatigue†	74 (22.6)	1 (0.3)	43 (13.3)	2 (0.6)	80 (38.5)	10 (4.8)
Diarrhea	70 (21.4)	1 (0.3)	38 (11.7)	0	179 (86.1)	17 (8.2)
Nausea	56 (17.1)	1 (0.3)	42 (13.0)	0	101 (48.6)	4 (1.9)
Arthralgia	46 (14.1)	2 (0.6)	46 (14.2)	1 (0.3)	19 (9.1)	1 (0.5)
Aspartate aminotransferase increase	41 (12.5)	3 (0.9)	41 (12.7)	3 (0.9)	34 (16.3)	5 (2.4)
Back pain	35 (10.7)	2 (0.6)	23 (7.1)	1 (0.3)	10 (4.8)	1 (0.5)
Alanine aminotransferase increase	34 (10.4)	1 (0.3)	33 (10.2)	2 (0.6)	28 (13.5)	10 (4.8)
Anemia†	33 (10.1)	7 (2.1)	41 (12.7)	9 (2.8)	91 (43.8)	16 (7.7)
Abdominal pain†	29 (8.9)	1 (0.3)	18 (5.6)	2 (0.6)	41 (19.7)	4 (1.9)
Vomiting	29 (8.9)	2 (0.6)	16 (4.9)	1 (0.3)	65 (31.2)	1 (0.5)
Decreased appetite	26 (8.0)	1 (0.3)	12 (3.7)	1 (0.3)	41 (19.7)	2 (1.0)
Thrombocytopenia†	18 (5.5)	3 (0.9)	16 (4.9)	4 (1.2)	38 (18.3)	3 (1.4)
Neutropenia†	17 (5.2)	7 (2.1)	15 (4.6)	6 (1.9)	100 (48.1)	41 (19.7)
Leukopenia†	17 (5.2)	2 (0.6)	15 (4.6)	0	54 (26.0)	9 (4.3)
Rash†	9 (2.8)	0	12 (3.7)	0	21 (10.1)	3 (1.4)
Hypercreatinemia†	9 (2.8)	1 (0.3)	7 (2.2)	0	45 (21.6)	2 (1.0)

Imlunestrant Monotherapy:
Dose Reduction Rate: 2.4%
Discontinuation Rate: 4.3%

Imlunestrant + Abemaciclib:
Dose Reduction Rate: 39.4%
Discontinuation Rate: 6.3%

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Oral SERDs for HR+/HER2- Metastatic Breast Cancer

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- Imlunestrant alone and with abemaciclib (**EMBER3**)
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- Emerging oral SERD combination regimens and key trials
- Summary, key questions, future directions

evERA: Phase III Giredestrant + Everolimus

A global, randomised, open-label, Phase III trial

Key eligibility criteria*

- ER+, HER2– aBC (1–3L of therapy)
- ≤ 2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

Enrolment period: August 2022 to October 2024

N = 373*

R 1:1

Giredestrant (30 mg) + everolimus (10 mg)†

SOC ET‡ + everolimus (10 mg)†
‡Exemestane/fulvestrant/tamoxifen

Until PD or unacceptable toxicity

† Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)

Stratification factors

- Prior treatment with fulvestrant (yes vs no)
- *ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

Co-primary endpoints (RECIST v1.1)

- INV-PFS in patients whose tumours had *ESR1*m
- INV-PFS in the ITT population

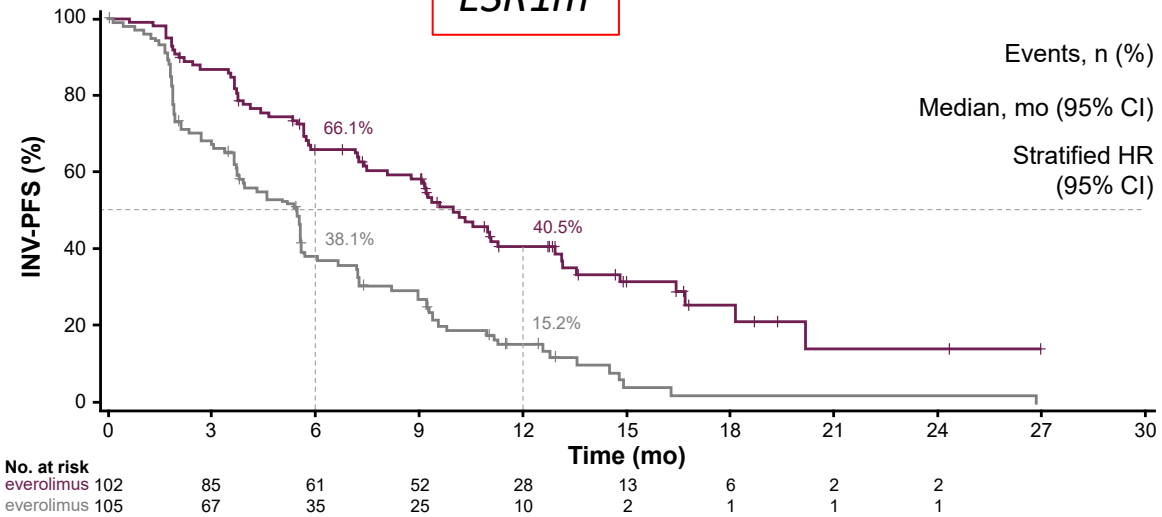
Key secondary endpoints

- OS
- INV-assessed ORR, DoR

ClinicalTrials.gov number, NCT05306340. Adapted from Mayer EL, *et al.* SABCS 2022 (poster OT2-01-07) with permission.

evERA: Phase III Giredestrant + Everolimus, Efficacy

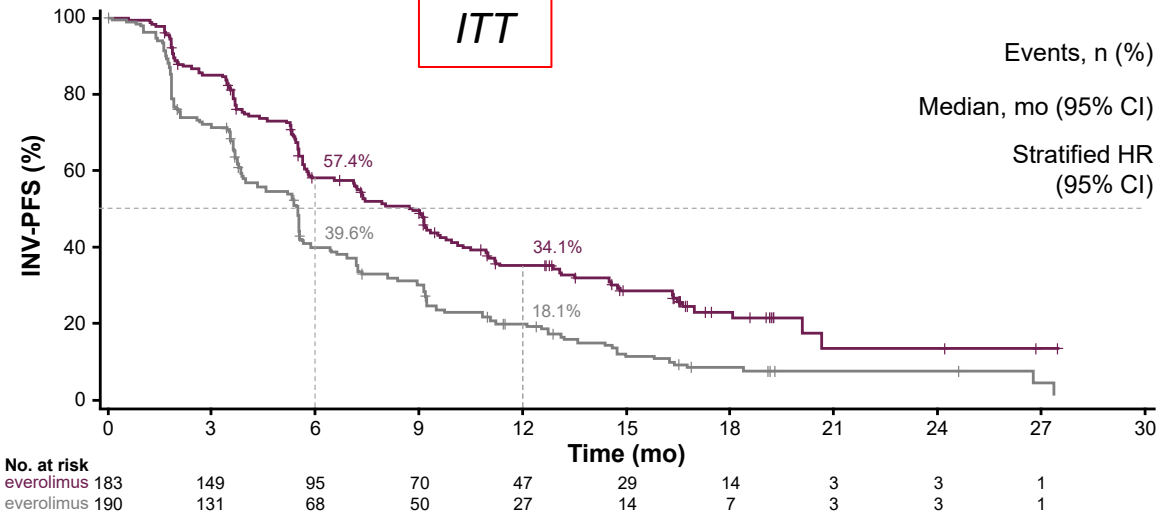
ESR1m



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

55.5% ESR1m Overall

ITT



	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	8.77 (6.60, 9.59)	5.49 (4.01, 5.59)
Stratified HR (95% CI)	**0.56** (0.44, 0.71); p < 0.0001	

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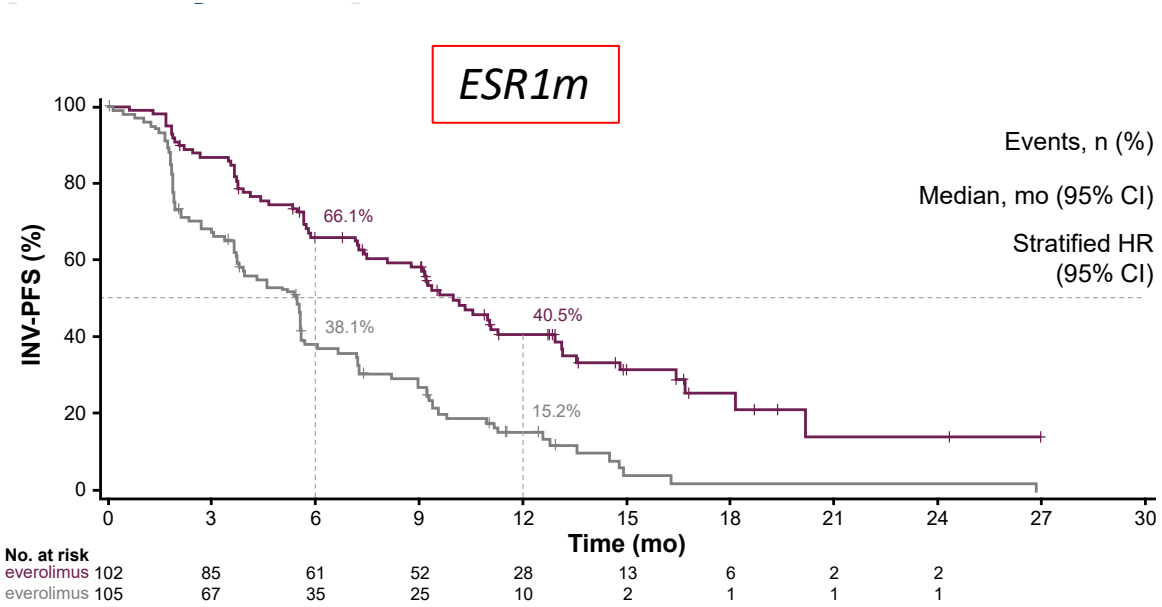
evERA: Phase III Giredestrant + Everolimus, Efficacy

ESR1m

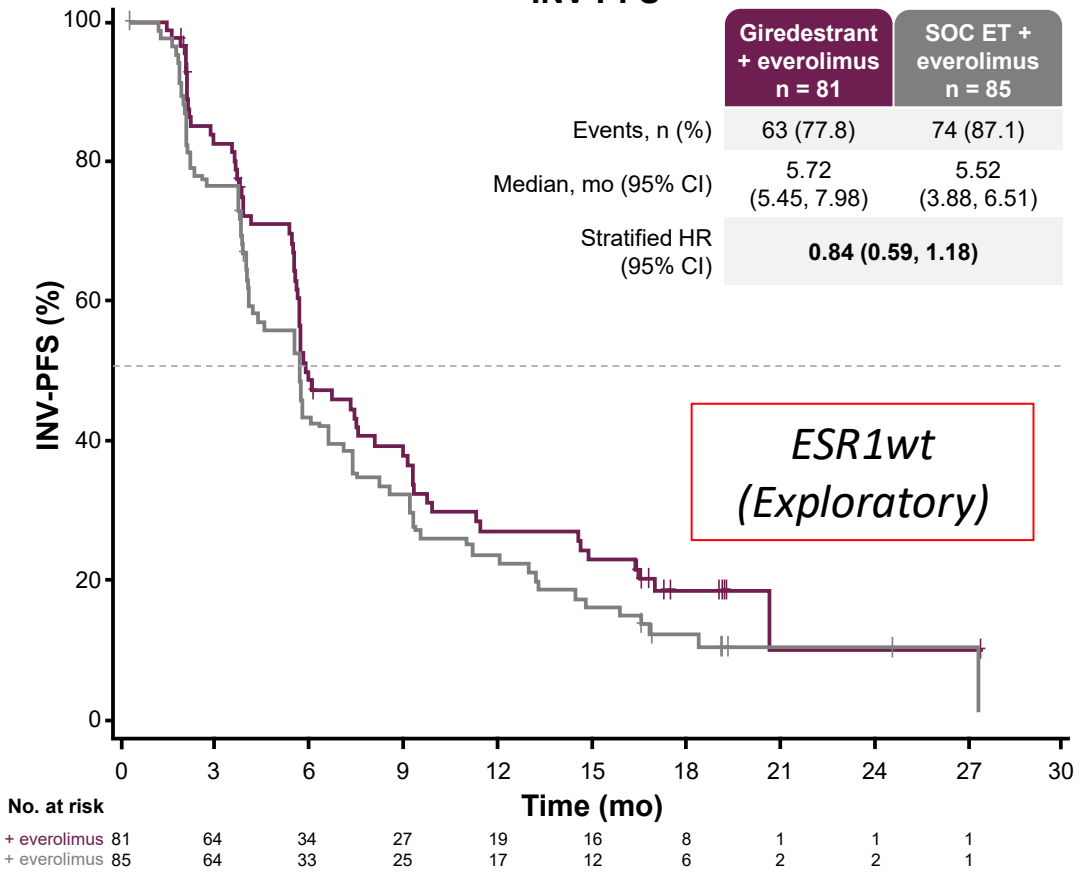


	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

55.5% ESR1m Overall

INV-PFS

	Giredestrant + everolimus n = 81	SOC ET + everolimus n = 85
Events, n (%)	63 (77.8)	74 (87.1)
Median, mo (95% CI)	5.72 (5.45, 7.98)	5.52 (3.88, 6.51)
Stratified HR (95% CI)	**0.84 (0.59, 1.18)**	



ESR1wt (Exploratory)

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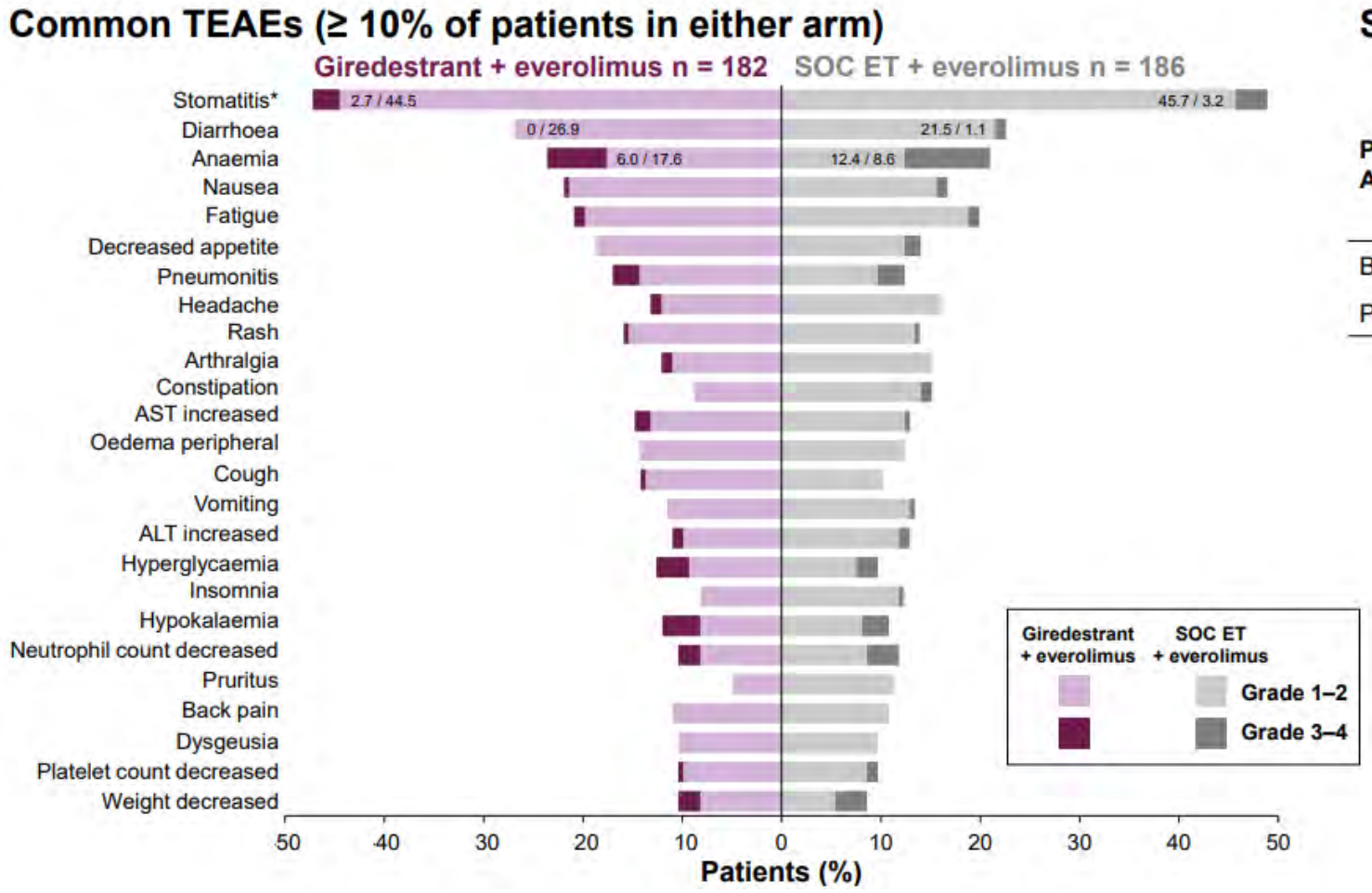
evERA: Phase III Giredestrant + Everolimus, Toxicity



Selected AEs

Patients with AE, n	Giredestrant + everolimus n = 182		SOC ET + everolimus n = 186	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Bradycardia†	7 (3.8)	0	1 (0.5)	0
Photopsia	0	0	0	0

Giredestrant + Everolimus:

Discontinuation Rate
Giredestrant: 8.2%
Everolimus: 17%

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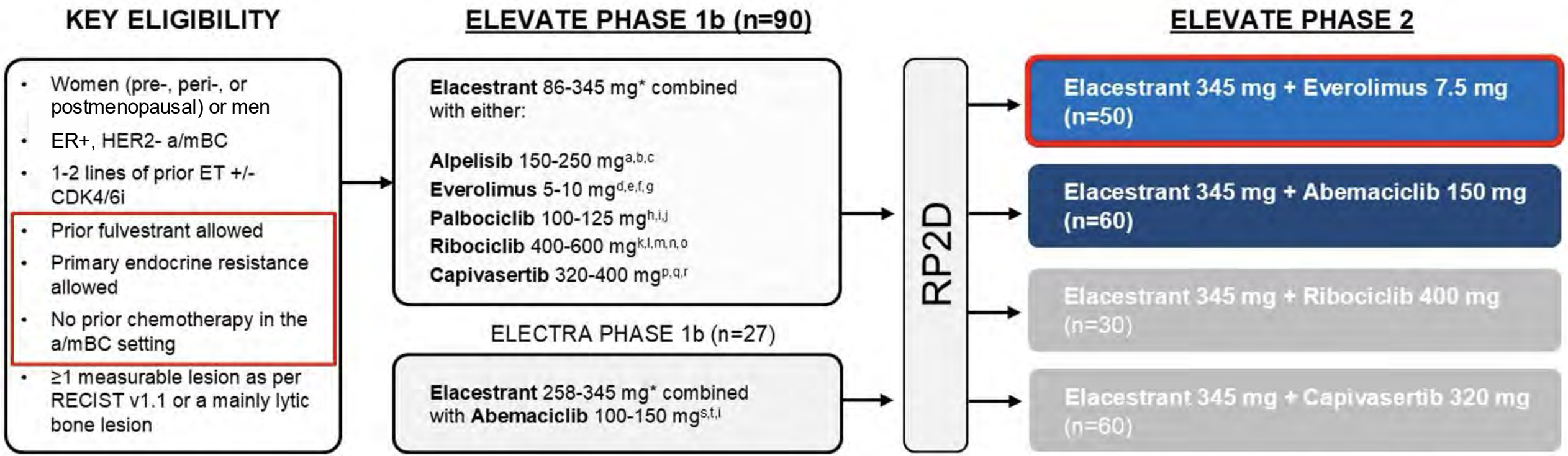
ELEVATE: Phase I/II Elacestrant Combinations



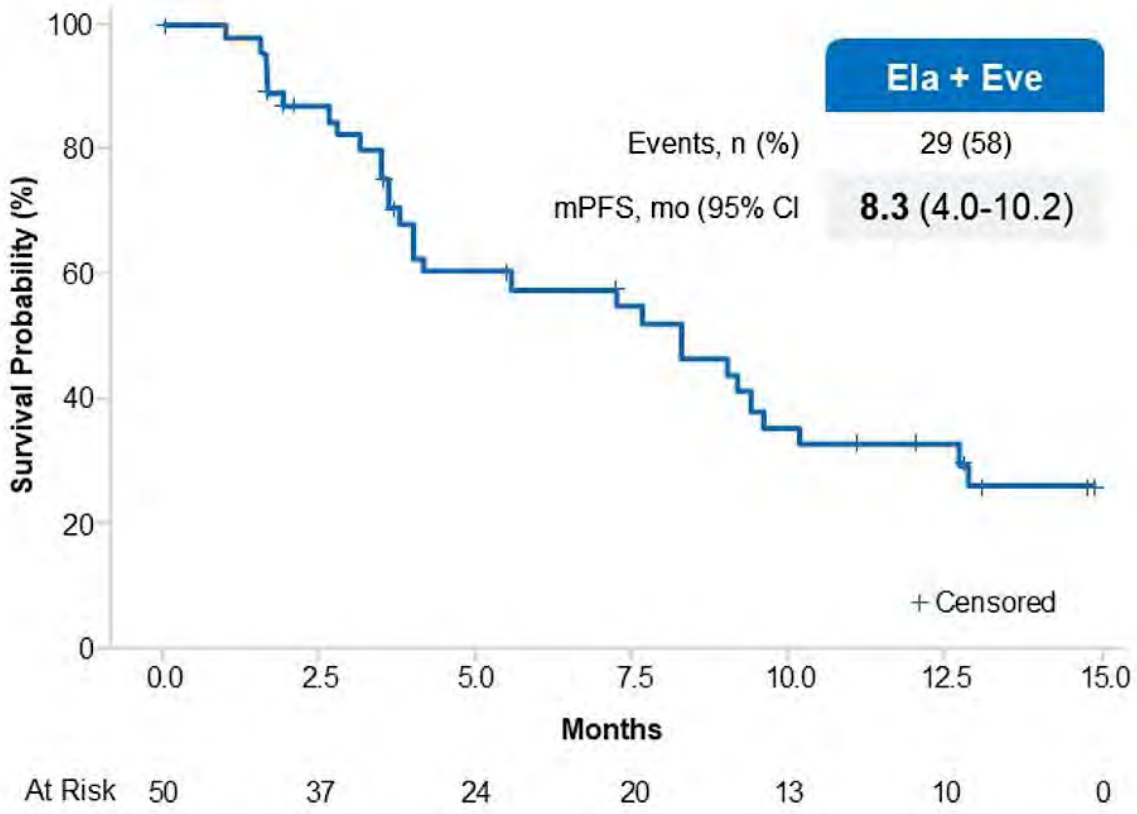
Phase 2 Objectives

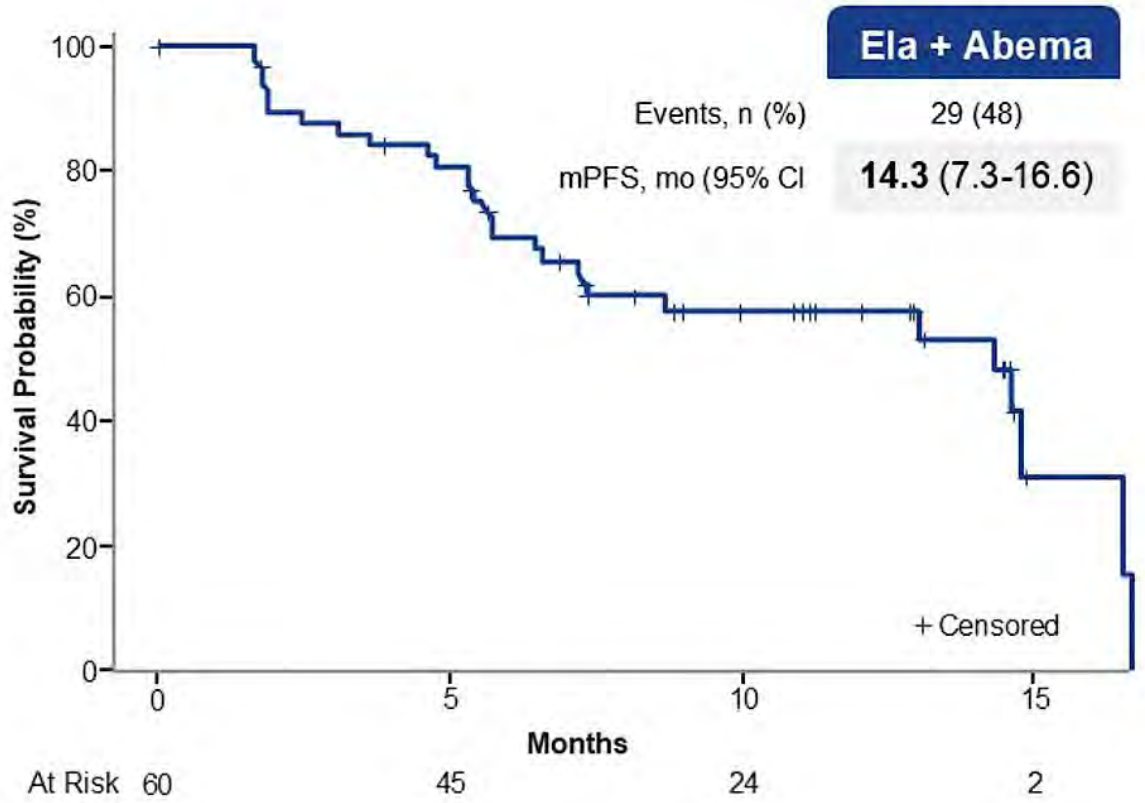
Primary: PFS (RECIST v1.1)

Secondary: ORR, DoR, CBR, PFS, OS, and safety

Elacestrant and everolimus dose are administered QD. Abemaciclib is administered BID.

ELEVATE: Phase I/II Elacestrant Combinations





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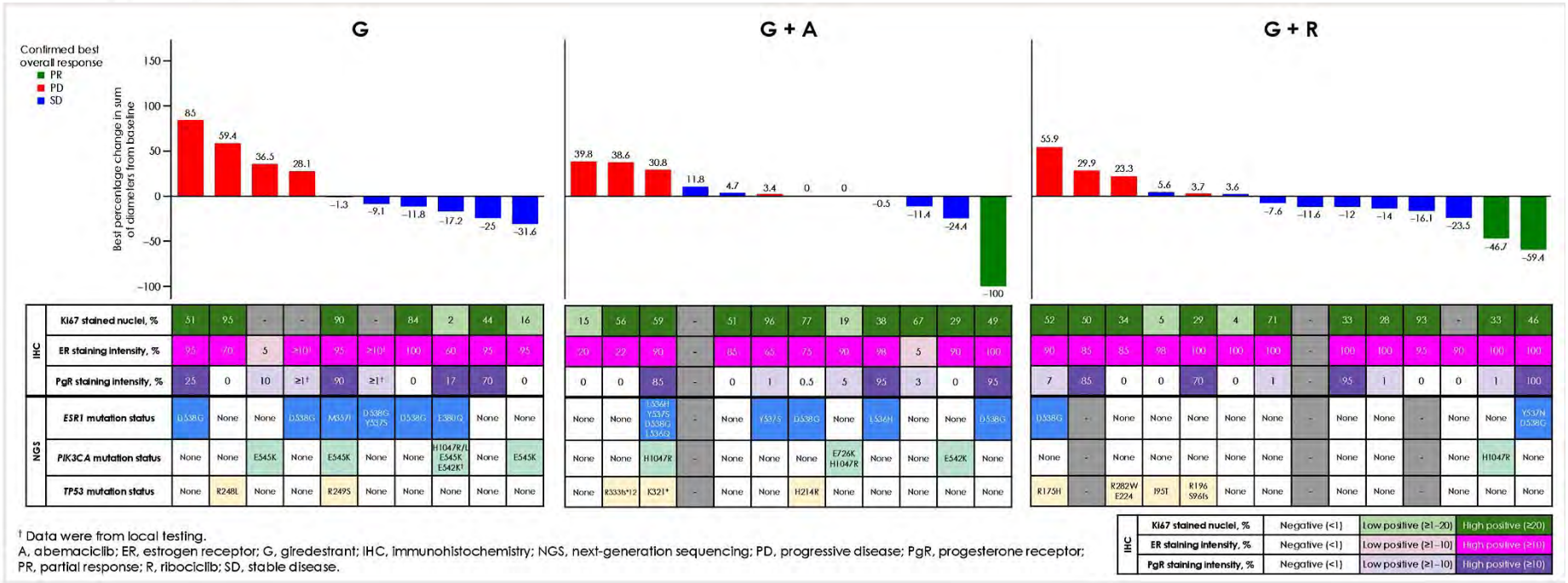
MORPHEUS: Phase I/II Giredestrant Combinations

Primary endpoints

- ORR (percentage of pts with CR or PR)‡
- Safety
- Pharmacokinetics

Secondary efficacy endpoints

- PFS‡
- DCR (percentage of pts with SD for ≥12 weeks, CR, or PR)‡
- CBR (percentage of pts with SD for ≥24 weeks, CR, or PR)‡
- OS
- DoR‡



† Data were from local testing.
A, abemaciclib; ER, estrogen receptor; G, giredestrant; IHC, immunohistochemistry; NGS, next-generation sequencing; PD, progressive disease; PgR, progesterone receptor; PR, partial response; R, ribociclib; SD, stable disease.

IHC				
	Ki67 stained nuclei, %	Negative (<1)	Low positive (≥1–20)	High positive (≥20)
	ER staining intensity, %	Negative (<1)	Low positive (≥1–10)	High positive (≥10)
	PgR staining intensity, %	Negative (<1)	Low positive (≥1–10)	High positive (≥10)

Oliveira M et al ASCO 2023

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- Summary, key questions, future directions

Current and Evolving Therapeutic Landscape: ER+ MBC

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

Fulvestrant + Palbo
+ Inavolisib
(*PIK3CAm*,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib
Antiestrogen + Everolimus
(*NGS Negative*)

Fulvestrant + Alpelisib
(*PIK3CAm*)

Fulvestrant + Capivasertib
(*PIK3CAm, AKTm, PTENm*)

Elacestrant or Imlunestrant
(*ESR1m*)

Olaparib
(*BRCAm*)

3rd Line (and beyond)::
Trastuzumab Deruxtecan (ADC, HER2-low)
Chemotherapy (many choices)
Sacituzumab Govitecan (ADC)
Datopotamab Deruxtecan (ADC)

Current and Evolving Therapeutic Landscape: ER+ MBC

(+) Phase III Data (not yet approved)
Camizestrant Switch via ESR1 ctDNA?

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

Fulvestrant + Palbo
+ Inavolisib
(*PIK3CAm*,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib
Antiestrogen + Everolimus
(*NGS Negative*)

Fulvestrant + Alpelisib
(*PIK3CAm*)

Fulvestrant + Capivasertib
(*PIK3CAm, AKTm, PTENm*)

Elacestrant or Imlunestrant
(*ESR1m*)

Olaparib
(*BRCAm*)

3rd Line (and beyond)::
Trastuzumab Deruxtecan (ADC, HER2-low)
Chemotherapy (many choices)
Sacituzumab Govitecan (ADC)
Datopotamab Deruxtecan (ADC)

**Ongoing clinical trials exploring:
New antiestrogens (KAT6i) and doublets/triplets
New CDK4/2 inhibitors
New targeted agents (PI3K, RAS pathway)
New ADCs

(+) Phase III Data (not yet approved)
Single Agent: Vepdegestrant? ESR1m?

Doublet/Triplet:
Imlunestrant + Abemaciclib? NGS agnostic?
Giredestrant + Everolimus? ESR1m?
Gedatolisib + Fulvestrant +/- Palbociclib? NGS agnostic?

Summary, Key Questions, and Future Directions

- ESR1 mutations emerge under selective pressure during estrogen deprivation; rare in primary tumors and untreated metastatic disease

- EMERALD: elacestrant monotherapy has activity in ESR1m disease; improved outcomes in patients with longer duration on 1st line ET/CDK4/6i
- Real world data suggests median TTNT 6-9 months on elacestrant; inferior outcomes with concurrent ESR1/PIK3CAm; equivalent activity in ESR1 Y537S

- EMBER3: imlunestrant monotherapy with activity in ESR1m; doublet therapy with abemaciclib provokes benefit ~9-10 months (regardless of prior CDK4/6i progression)

- evERA: giredestrant and everolimus doublet demonstrated significant benefit compared to standard ET and everolimus in patients with ESR1m (also 9-10 months)

- Oral SERDs are well tolerated, without increased safety signals in combination regimens

Summary, Key Questions, and Future Directions

- Is there a role for oral SERD monotherapy in HR+/HER2- metastatic breast cancer? How can we identify those patients likely to have durable responses to single agent?
- How will earlier deployment of next-generation antiestrogens (eg adjuvant) impact resistance landscape?

- Which doublet and triplet regimens will provoke the most benefit? Combinations with CDKi, PI3K/AKTi?
  - When should they be deployed (1st line, 2nd line, later)?

- How should we approach patients without actionable genomic changes in the 2nd line? Will a next-generation antiestrogen have a role in this population?

- Dynamic changes in ctDNA level and targetable alterations (eg. ESR1) are likely to become part of routine clinical decision-making. How will SERENA6 enter clinical practice?

- Ongoing efforts (multigene and transcriptional signatures) will refine our ability to predict ER-dependence, and promote better personalization for patients in the 2nd-3rd line metastatic setting

QUESTIONS?

Module 10: HR-Positive Breast Cancer

Current and Future Management of HR-Positive, HER2-Negative Localized Breast Cancer — Dr Meisel

Optimizing First-Line Therapy for Patients with HR-Positive mBC — Dr Hamilton

Current and Future Role of Oral SERDs for Progressive HR-Positive mBC — Dr Wander

Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr O'Shaughnessy

Clinical Utility of Agents Targeting the PIK/AKT/mTOR Pathway for Patients with Progressive HR-Positive MBC

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Baylor University Medical Center
Texas Oncology
Sarah Cannon Research Institute
Dallas TX

Disclosures

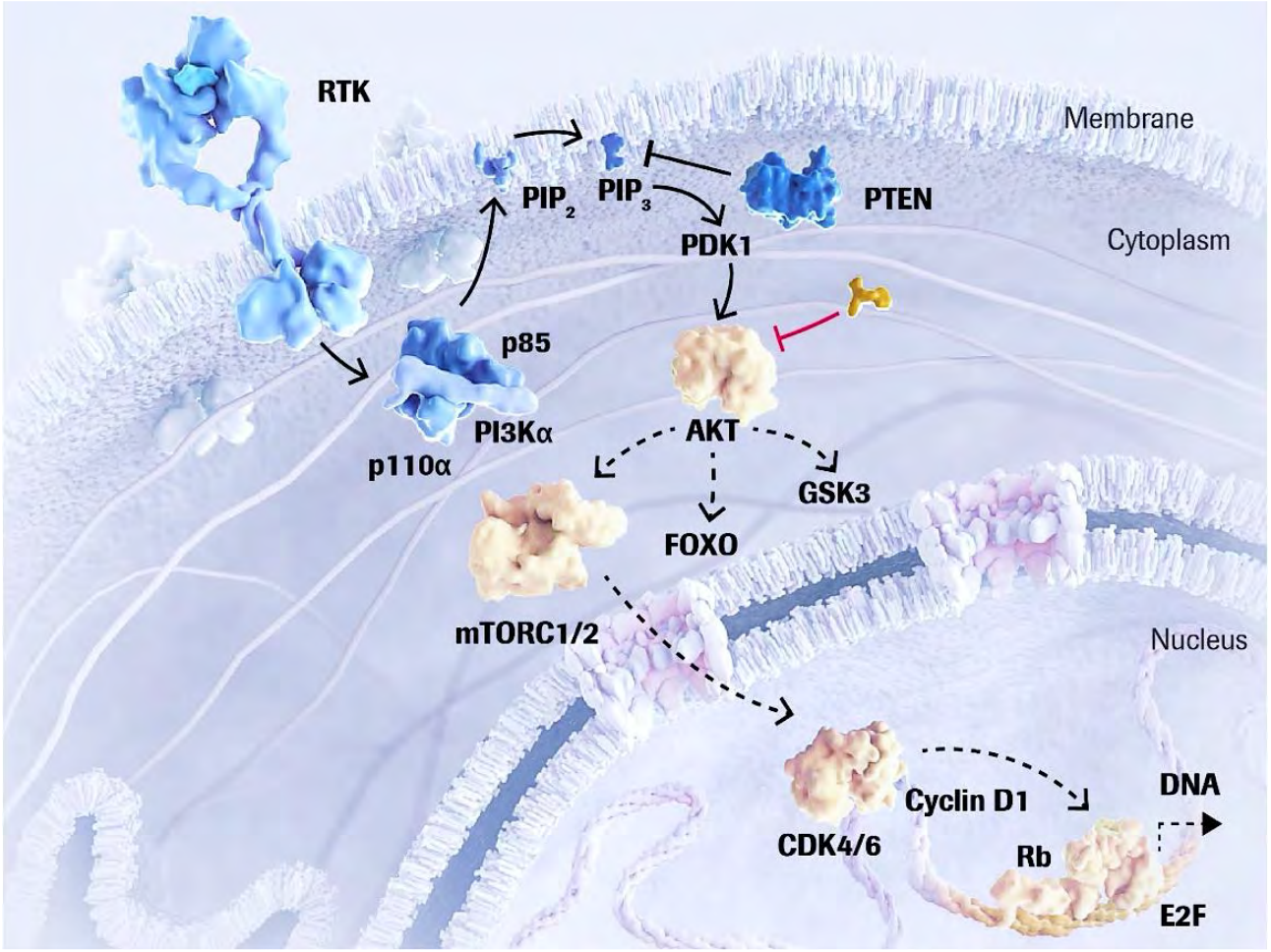
Advisory Committees and Consulting Agreements	Aadi Bioscience, Agendia Inc, Amgen Inc, Aptitude Health, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Daiichi Sankyo Inc, Duality Biologics, Eisai Inc, Ellipses Pharma, Exact Sciences Corporation, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, HiberCell, Jazz Pharmaceuticals Inc, Johnson & Johnson, Lilly, Menarini Group, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Pfizer Inc, Pierre Fabre, Puma Biotechnology Inc, RayzeBio, Roche Laboratories Inc, Sanofi, Seagen Inc, Stemline Therapeutics Inc, Summit Therapeutics, Tempus, TerSera Therapeutics LLC

PIK3, AKT and mTOR as Therapeutic Targets[1]

Mechanisms of PIK3CA/AKT Activation

- Loss of function of negative regulators
  - PTEN, INPP4B, PHLPP, PP2A
- Gain of function of positive regulators
  - PI3K, AKT, RTKs (eg, HER2)
- Therapy-induced survival response
  - Chemotherapy, endocrine therapy

PIK3CA/AKT/mTOR Pathway



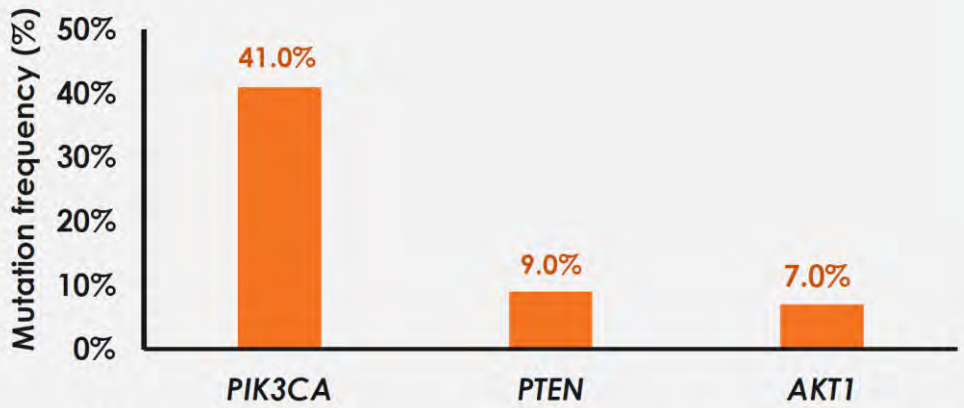
1. Dent R et al. SABCS 2020. Presentation GS3-04.

Prevalence of *PIK3CA*, *AKT* and *PTEN* alterations in HR+ MBC

Frequency of AKT Pathway Alterations in HR+/HER2- mBC	
Alteration	**Frequency**
PIK3CA mutation	28–46%[1-5]
AKT1 mutation	1–11%[1-5]
PTEN mutation	1–14%[1-4]

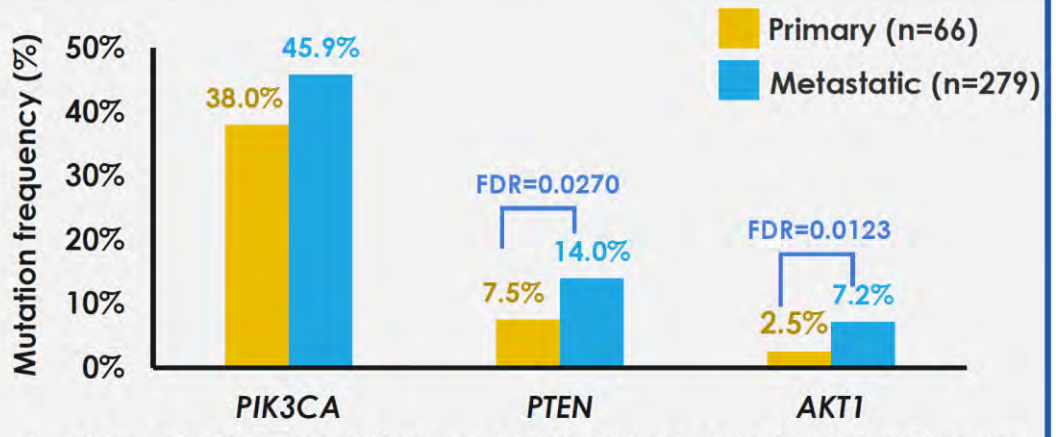
- Further research is required to understand to what extent exposure to CDK4/6i-ET treatment increases the frequency of AKT-pathway mutations, as *PTEN*, *AKT1* and *PIK3CA* alterations have been observed pre- and post-exposure.[1,2,8,9,11,12]
- Testing of metastatic tissue is preferred to inform mBC treatment decisions.[13,14]

Mutation frequency in prospectively sequenced HR+/HER2- BC samples (n=1,501) at a single US centre[12]



- 762 metastatic tumours (Stage I–IV at diagnosis) with prior ET from the prospective cohort vs. 739 primary tumours from TCGA
- Mutation frequencies were similar between primary and metastatic tissue*

Mutation frequency in prospectively collected HR+/HER2- BC samples from 49 centres in The Netherlands[1,2]



- 279 metastatic tumours from prospective collection vs. 66 primary tumours from TCGA and BASIS
- *PTEN* and *AKT1* were more frequently mutated in metastatic vs. primary BC (FDR<0.05)

Angus L et al *Nat Genet.* 2019. Mosele F et al *Ann Oncol.* 2020. Chung JH et al *Ann Oncol.* 2017. Pezo RC et *al Breast Cancer Res Treat.* 2018. Paul MR et al. *Clin Invest.* 2020. Bertucci F et al. *Nature.* 2019. O'Leary B et al *Cancer Discov.* 2018. Wander SA et al. *Cancer Discov.* 2020. Miller TW et al *J Clin Invest.* 2010. Rosin J et al *Breast Cancer Res Treat.* 2023. Razavi P et al. *Cancer Cell.* 2018. NCCN. Breast Cancer. Version 1.2024. Published online January 25, 2024. Burstein HJ *JCO* 2023.

CAPItello-291:

Phase III, randomized, double-blind, placebo-controlled study

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression 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

43.7% altered

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*

Placebo — Twice daily, 4 days on, 3 days off

37% altered

Fulvestrant — 500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

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

Overall survival
- Overall
- AKT pathway-altered tumors

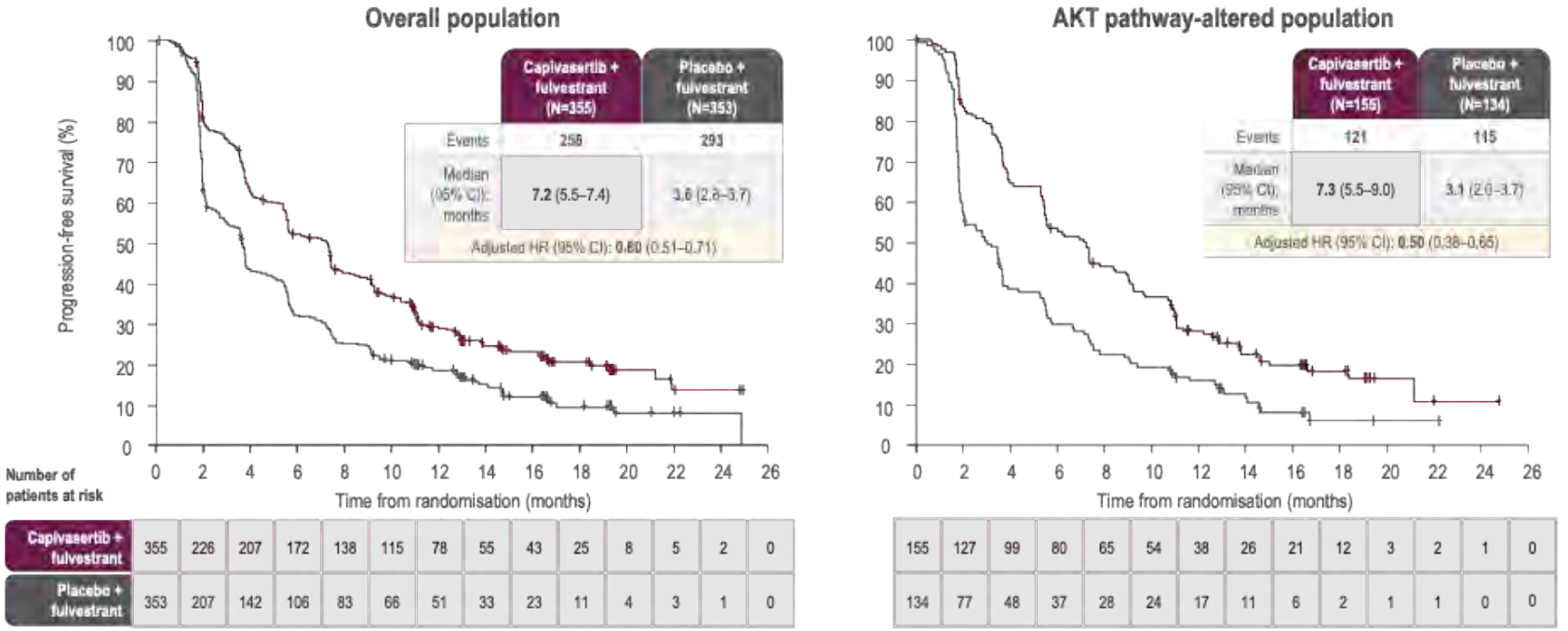
Objective response rate
- Overall
- AKT pathway-altered tumors

Summary of Demographics

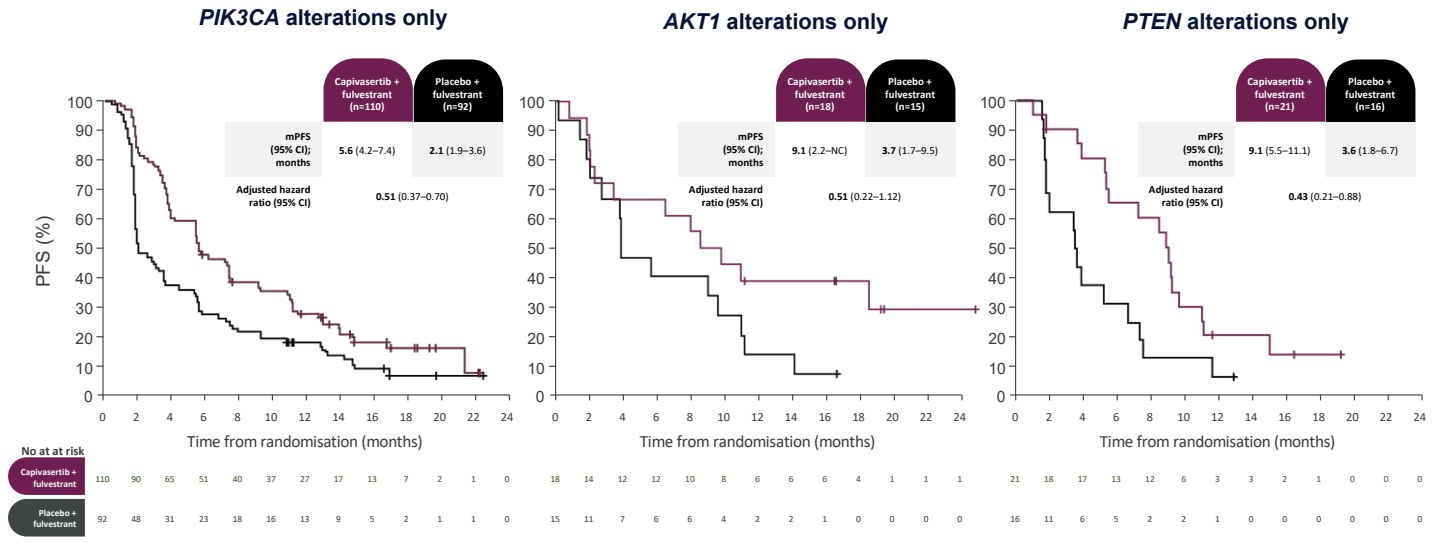
- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

Turner et al, NEJM 2023;388(22):2058-2070.

Capitello-291: Efficacy Results



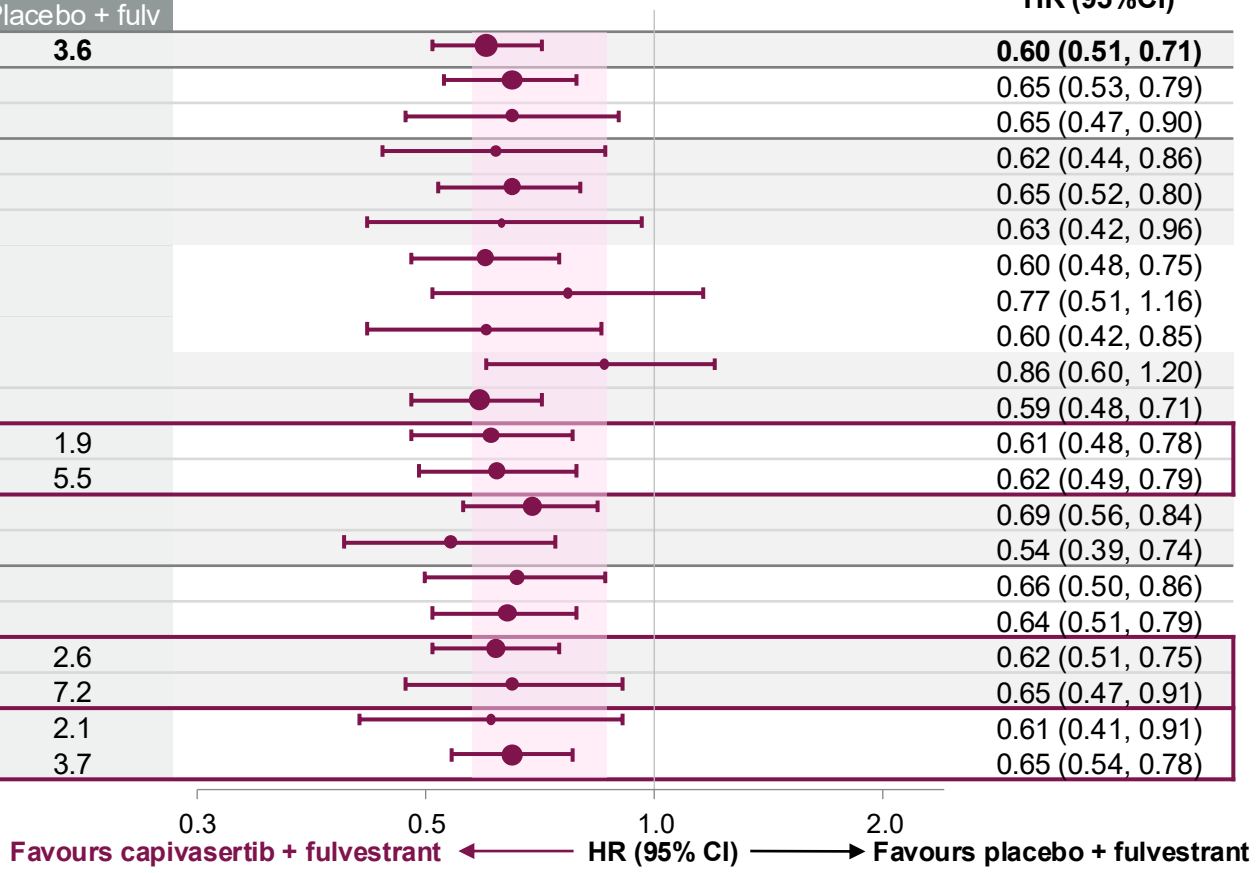
Exploratory analysis of PFS in patients by alteration type (Global population)



Turner et al, NEJM 2023;388(22):2058-2070;
Howell S et al. SABCS 2023;Abstract PS17-03.

CAPItello-291: Summary of PFS by Subgroup (Overall Population)[1]

		Number of patients	mPFS (months)[2]		HR (95%CI)
			Capi + fulv	Placebo + fulv	
All patients		**708**	**7.2**	**3.6**	**0.60 (0.51, 0.71)**
Age	<65 years	491			0.65 (0.53, 0.79)
	≥65 years	217			0.65 (0.47, 0.90)
Race	Asian	189			0.62 (0.44, 0.86)
	White	407			0.65 (0.52, 0.80)
	Other	112			0.63 (0.42, 0.96)
Region	1	395			0.60 (0.48, 0.75)
	2	136			0.77 (0.51, 1.16)
	3	177			0.60 (0.42, 0.85)
Menopausal status (females only)	Pre/peri	154			0.86 (0.60, 1.20)
	Post	547			0.59 (0.48, 0.71)
Liver metastases at baseline	Yes	306	3.8	1.9	0.61 (0.48, 0.78)
	No	402	9.2	5.5	0.62 (0.49, 0.79)
Visceral metastases	Yes	478			0.69 (0.56, 0.84)
	No	230			0.54 (0.39, 0.74)
Endocrine resistance	Primary	262			0.66 (0.50, 0.86)
	Secondary	446			0.64 (0.51, 0.79)
Prior use of CDK4/6is	Yes	496	5.5	2.6	0.62 (0.51, 0.75)
	No	212	10.9	7.2	0.65 (0.47, 0.91)
Prior chemotherapy for aBC	Yes	129	3.8	2.1	0.61 (0.41, 0.91)
	No	579	7.3	3.7	0.65 (0.54, 0.78)

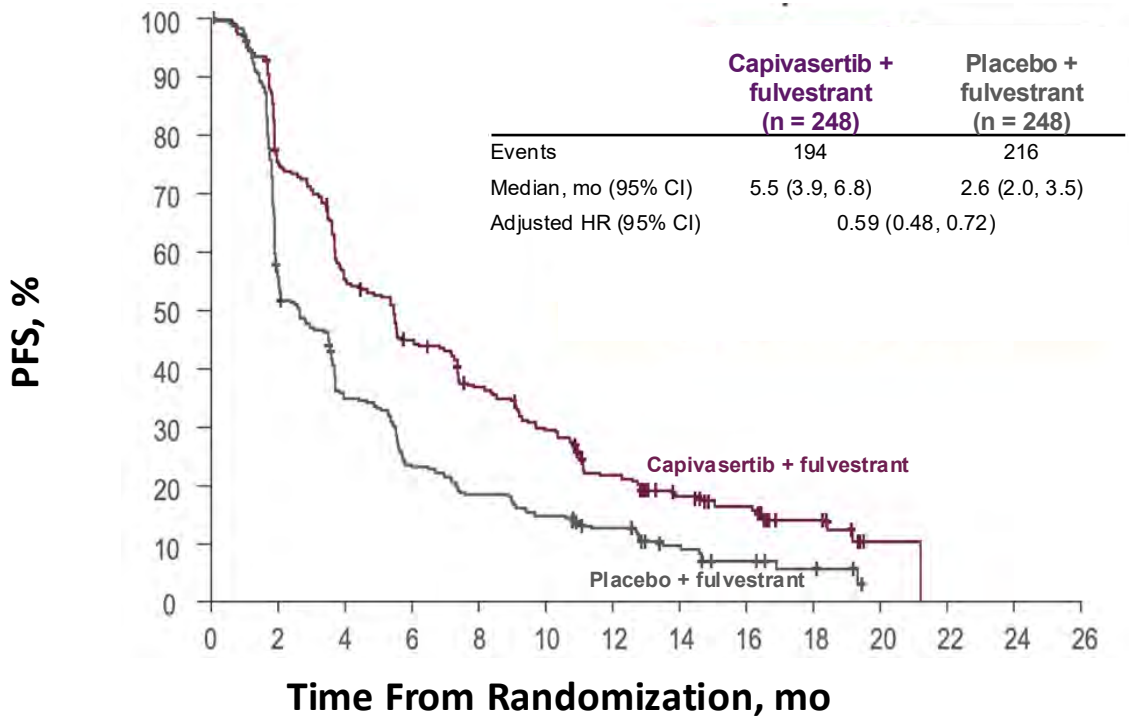


PFS benefit for capivasertib + fulvestrant compared with placebo + fulvestrant **was seen across key clinically relevant subgroups**, including overall and *PIK3CA/AKT1/PTEN*-altered populations, prior CDK4/6i treatment and in patients with liver metastases [1,2]

Data cut-off: August 2022. PFS results were comparable in the *PIK3CA/AKT1/PTEN*-altered population.
AKT1 = AKT serine/threonine kinase 1 (gene); CDK4/6i = cyclin dependent kinase 4/6 inhibitor; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene); *PTEN* = phosphatase and tensin homologue (gene).
1. Adapted from Turner NC et al. Article and supplementary appendix. *N Engl J Med*. 2023;388(22):2058–2070. 2. Turner NC et al. Presented at ESMO Breast Cancer Annual Congress, May 11–13, 2023.

CAPItello-291: PFS by Prior CDK4/6 Inhibitor (Overall Population)[1]

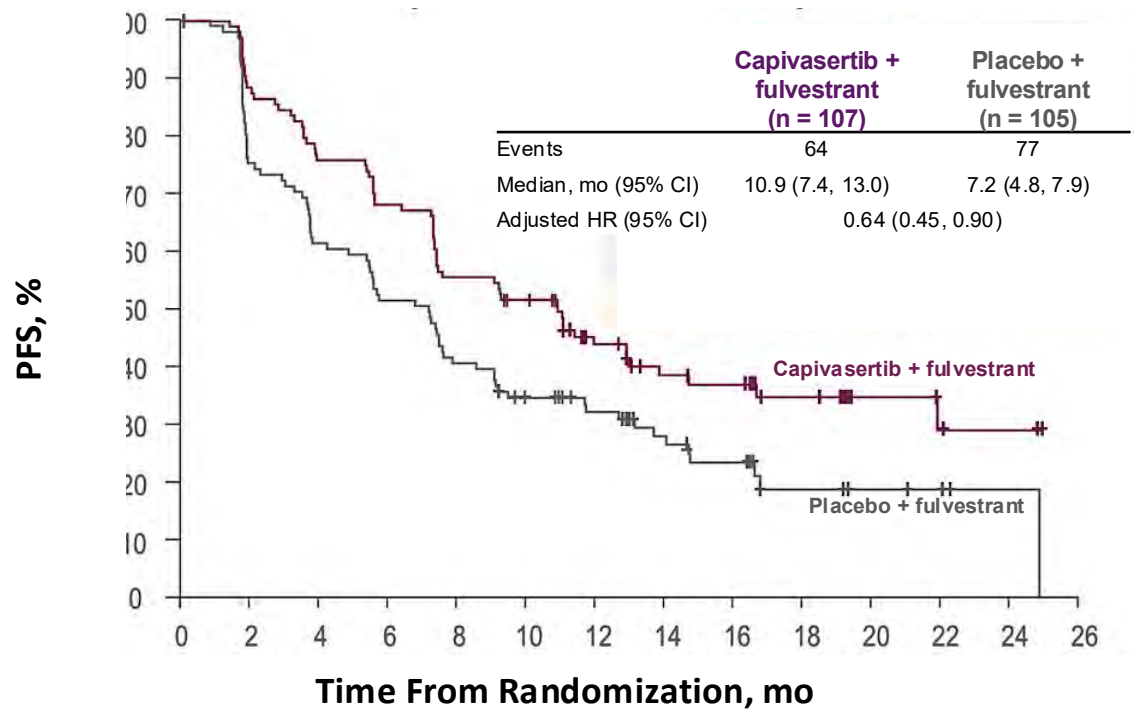
Prior CDK4/6 Inhibitor Exposure



	Capivasertib + fulvestrant (n = 248)	Placebo + fulvestrant (n = 248)
Events	194	216
Median, mo (95% CI)	5.5 (3.9, 6.8)	2.6 (2.0, 3.5)
Adjusted HR (95% CI)	0.59 (0.48, 0.72)	

No. at Risk														
Capivasertib + fulvestrant	248	175	129	102	81	64	43	29	21	10	1	0	0	0
Placebo + fulvestrant	248	131	80	54	42	34	25	14	8	4	0	0	0	0

No Prior CDK4/6 Inhibitor Exposure



	Capivasertib + fulvestrant (n = 107)	Placebo + fulvestrant (n = 105)
Events	64	77
Median, mo (95% CI)	10.9 (7.4, 13.0)	7.2 (4.8, 7.9)
Adjusted HR (95% CI)	0.64 (0.45, 0.90)	

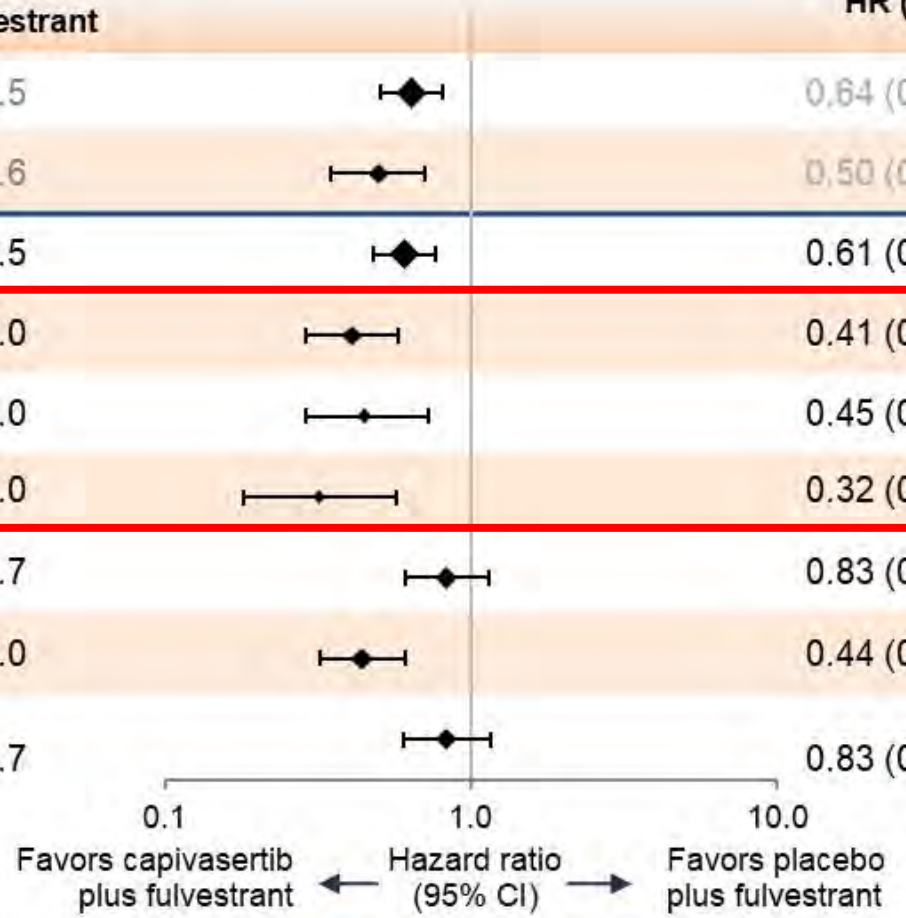
No. at Risk														
Capivasertib + fulvestrant	107	91	78	70	57	51	35	26	22	15	7	5	2	0
Placebo + fulvestrant	105	76	62	52	41	32	26	19	15	7	4	3	1	0

In the overall population, consistent clinically meaningful benefit with capivasertib + fulvestrant was observed in patients with and without prior CDK4/6 inhibitor exposure

1. Turner NC et al. ESMO Breast 2023. Abstract 1870.

Summary of PFS by ctDNA alteration status: restricted to post-1L ET + CDK4/6i for ABC*

	n	Median PFS (months) Capivasertib + fulvestrant	Median PFS (months) Placebo + fulvestrant	HR (95% CI)
Overall CAPItello-291 population	370	5.6	3.5	0.64 (0.51–0.81)
PIK3CA/AKT1/PTEN-altered by tissue	155	7.0	2.6	0.50 (0.35–0.71)
All patients with a ctDNA result	353	5.6	3.5	0.61 (0.48–0.77)
PIK3CA/AKT1/PTEN alteration detected in ctDNA	161	7.0	2.0	0.41 (0.29–0.58)
*ESR1*m co-mutation	94	7.0	2.0	0.45 (0.29–0.73)
No *ESR1*m detected	67	7.4	2.0	0.32 (0.18–0.57)
PIK3CA/AKT1/PTEN alteration not detected in ctDNA	192	5.5	3.7	0.83 (0.61–1.14)
PIK3CA/AKT1/PTEN alteration detected in either tissue or ctDNA	196	7.0	2.0	0.44 (0.32–0.61)
PIK3CA/AKT1/PTEN alteration not detected (either both methods or with one unknown)	172	4.9	3.7	0.83 (0.60–1.16)



Data cutoff: August 15 2022. *restricted to patients who received one prior line of AI plus CDK4/6i for ABC (except two patients [one in each treatment arm] who received adjuvant AI followed by tamoxifen plus CDK4/6i for ABC) and no prior chemotherapy for ABC. 1L, first line; ABC, advanced breast cancer; AI, aromatase inhibitor; *AKT1*, AKT serine/threonine kinase; CDK, cyclin-dependent kinase; CI, confidence interval; ctDNA, circulating tumor DNA; *ESR1*m, estrogen receptor gene mutation; HR, hazard ratio; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

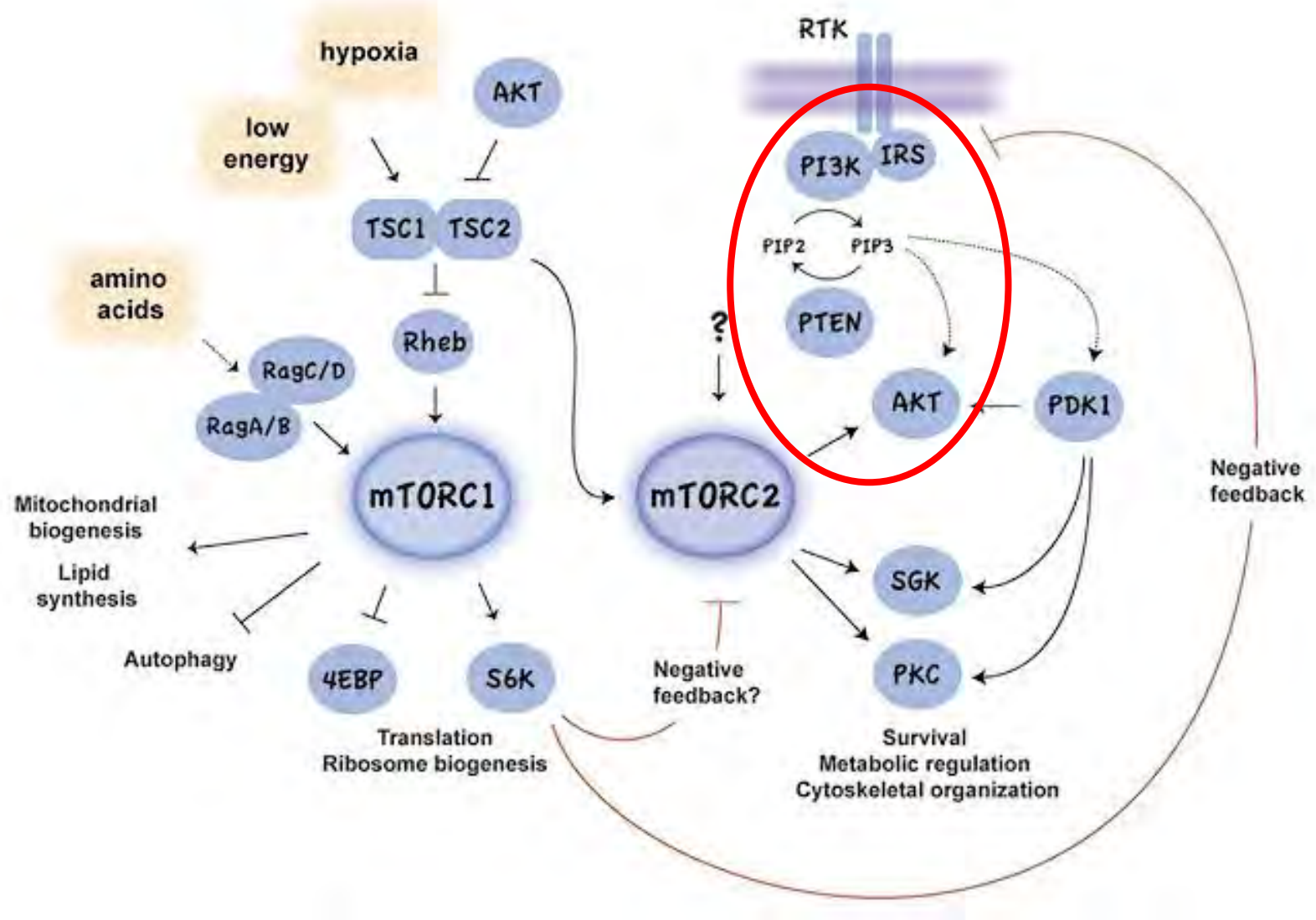
Turner NC et al. SABCS 2025.

Toxicity Summary: Everolimus, Capivasertib, Alpelisib, Inavolisib

	Alpelisib (PI3Ki)		Inavolisib (PI3Ki)		Capivasertib (AKTi)		Everolimus (mTORi)	
Toxicity	All grades	Grade 3+	All Grades	Grade 3+	All grades	Grade 3+	All grades	Grade 3+
Diarrhea %	57.7	6.7	48.1	3.7	72.4	9.3	30	2
Rash %	35.6	9.9	25.3	0	38	12.1	36	1
Hyperglycemia %	63.7	36.6	58.6	5.6	16.9	2	13	4
Stomatitis %	24.6	2.5	51.2	5.6	14.6	2	56	8
Discontinuation rate	25%		6.8%		13%		19%	

Rugo HS et al. *Ann Oncol*. 2020;31(8):1001-1010. Rugo HS et al. 2023 ASCO Annual Meeting. Abstract 1067. Baselga J et al. *N Engl J Med*. 2012;366(6):520-529. Jhaveri K et al 2023 SABCS.

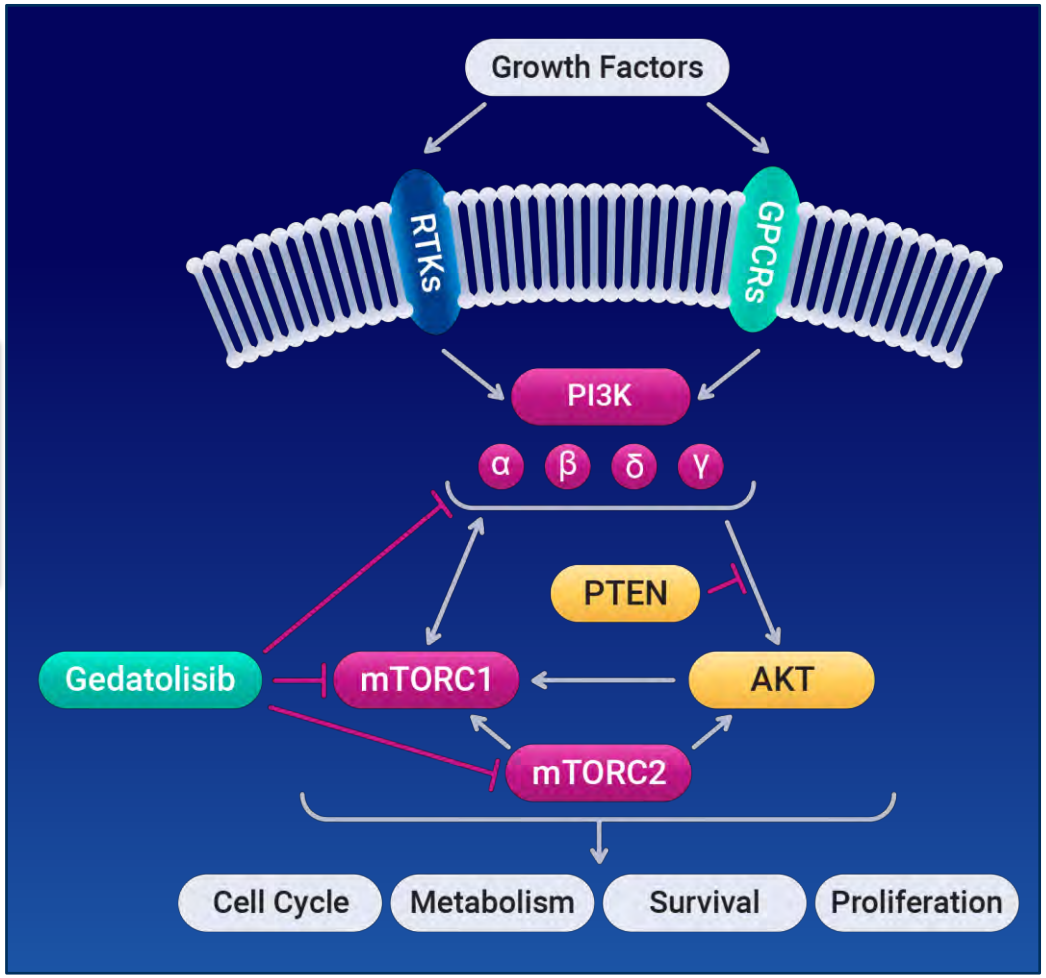
mTORC1 Inhibition Activates PI3K/AKT Signaling



Sparks CA et al. *Oncogene*. 2010;29(26):3733-3744.

Background on Gedatolisib: VIKTORIA-1 Trial

- The PI3K/AKT/mTOR (PAM) pathway drives breast cancer growth and contributes to endocrine and CDK4/6i resistance
  - Most available therapies are indicated only for patients with PI3K-pathway activation[1,2]
  - There remains a need for safe and effective therapies for those with *PIK3CA*-WT disease
- Gedatolisib, a highly potent multitarget PAM inhibitor of all class I PI3K isoforms, mTORC1, and mTORC2, has shown compelling preliminary clinical activity in combination with palbociclib & fulvestrant as 2L+ therapy in HR+/HER2- ABC
  - Median PFS of 12.9 months in all CDK4/6i-pretreated disease (n=27)[3]
  - Median PFS of 9.0 months in *PIK3CA*-WT disease (n=60)[4]
  - Median PFS of 14.6 months in *PIK3CA*-mutated disease (n=30)[4]
- We aimed to evaluate gedatolisib in patients with HR+/HER2- ABC after progression on a CDK4/6i and NSAI



Abbreviations: ABC, advanced breast cancer; AKT, protein kinase B; 2L, second-line; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; GPCRs, G protein-coupled receptors; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mTORC, mechanistic target of rapamycin complex; NSAI, non-steroidal aromatase inhibitor; PAM, PI3K/AKT/mTOR; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin entity; RTKs, receptor tyrosine kinases; WT, wild-type

1. Andre F. *N Engl J Med.* 2019;380:1929-40; 2. Turner NC. *N Engl J Med.* 2023;388:2058-70; 3. Layman R. *Lancet Oncol.* 2024;25:474-8; 4. Data on file, Celcuity Inc.: 65 of 90 patients (72%) had received prior treatment with a CDK4/6i inhibitor

Presenter: Sara A. Hurvitz, MD, FACP

VIKTORIA-1 Study Design

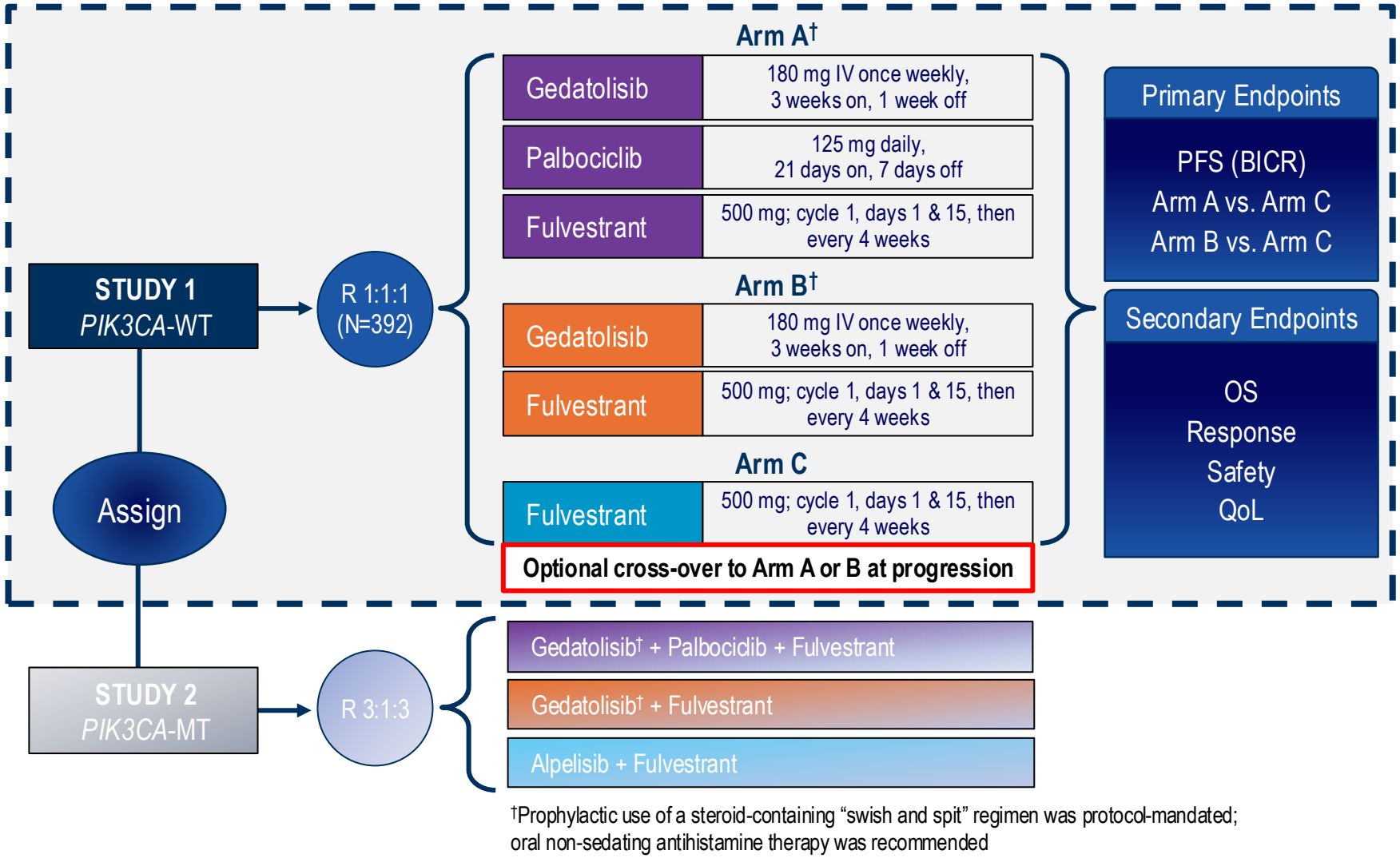
HR+/HER2- Advanced Breast Cancer

Eligibility Criteria

- Pre- & postmenopausal women & men
- **Progression on/after CDK4/6i + NSAI**
- ≤2 lines of prior ET for ABC
- Measurable disease, RECIST v1.1
- Screening result for *PIK3CA* status
- No T2DM with HbA1c >6.4% or T1DM
- No prior mTORi, PI3Ki, or AKTi
- No prior chemotherapy for ABC

Stratification Factors

- Lung/liver metastases (yes/no)
- TTP on immediate prior therapy (≤ or >6 months)
- Region (US/Canada or ROW)



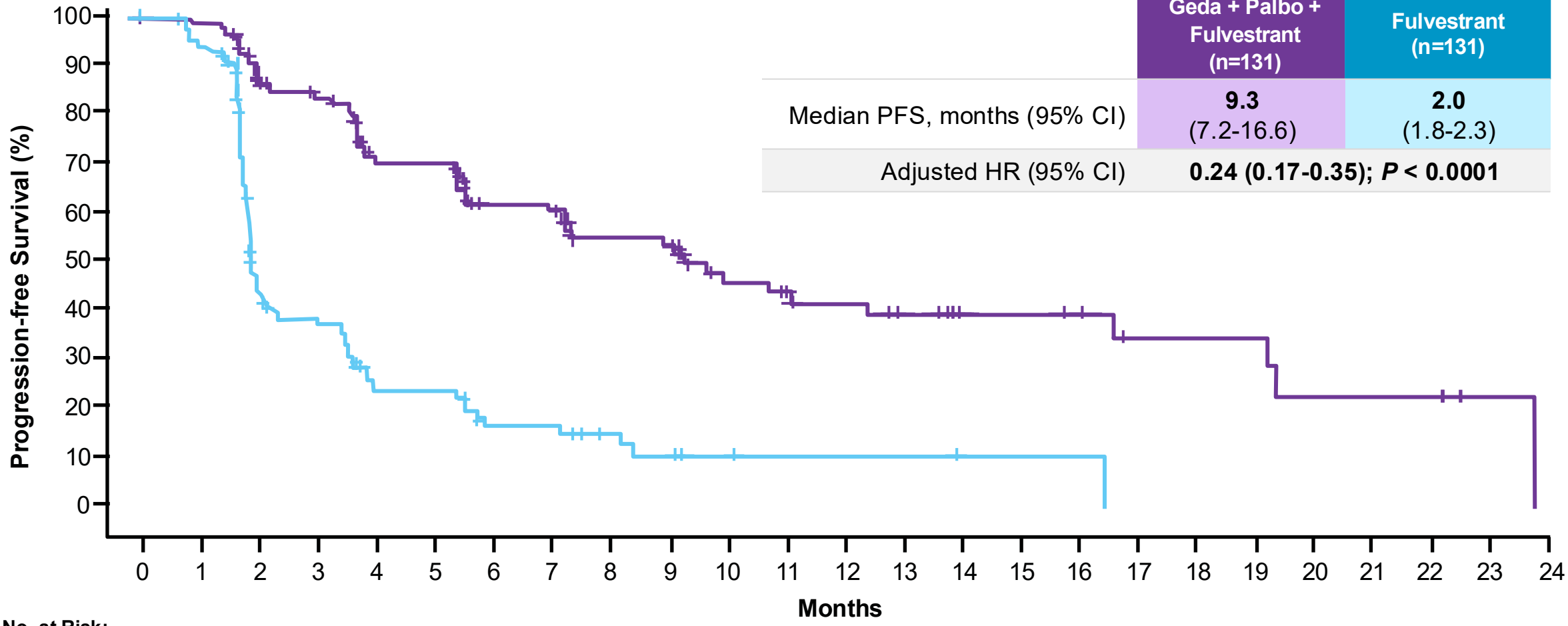
†Prophylactic use of a steroid-containing "swish and spit" regimen was protocol-mandated; oral non-sedating antihistamine therapy was recommended

Abbreviations: ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; ET, endocrine therapy; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IV, intravenous; MT, mutated; mTORi, mechanistic target of rapamycin inhibitor; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphatidylinositol 3-kinase inhibitor; QoL, quality of life; R, randomization; ROW, rest of world; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTP, time to progression; WT, wild-type

Presenter: Sara A. Hurvitz, MD, FACP

1st Co-Primary Endpoint: Progression-Free Survival

Gedatolisib Triplet vs. Fulvestrant, BICR Assessment



	Geda + Palbo + Fulvestrant (n=131)	Fulvestrant (n=131)
Median PFS, months (95% CI)	**9.3** (7.2-16.6)	**2.0** (1.8-2.3)
Adjusted HR (95% CI)	**0.24 (0.17-0.35); *P* < 0.0001**	

No. at Risk:

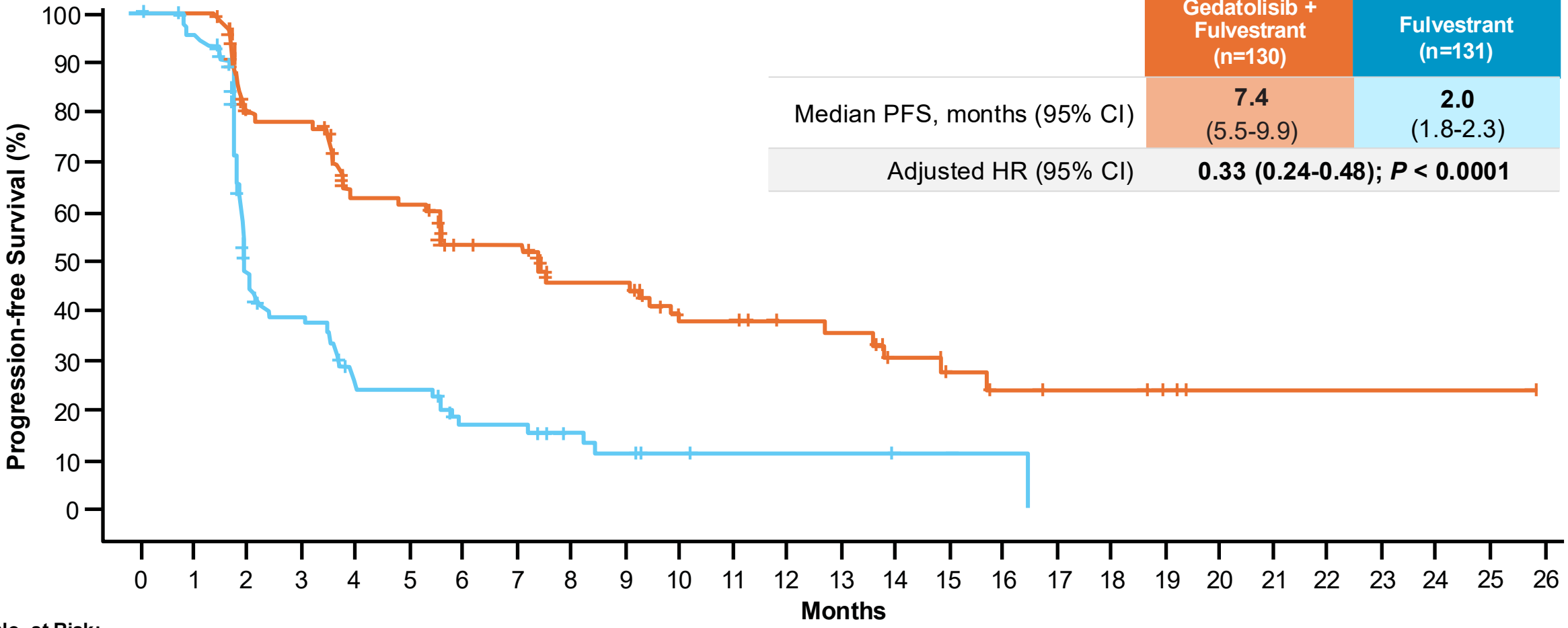
Geda + Palbo + Fulv	131	127	103	94	69	68	50	49	35	34	24	22	19	16	10	10	9	6	6	6	4	4	4	1	0
Fulv	131	114	45	35	20	20	11	11	7	5	3	2	2	2	1	1	1	0							

Presenter: Sara A. Hurvitz, MD, FACP

Hurvitz SA et al. *J Clin Oncol* 2026;44:1108-19.

2nd Co-Primary Endpoint: Progression-Free Survival

Gedatolisib Doublet vs. Fulvestrant, BICR Assessment



	Gedatolisib + Fulvestrant (n=130)	Fulvestrant (n=131)
Median PFS, months (95% CI)	**7.4** (5.5-9.9)	**2.0** (1.8-2.3)
Adjusted HR (95% CI)	**0.33 (0.24-0.48); *P* < 0.0001**	

No. at Risk:

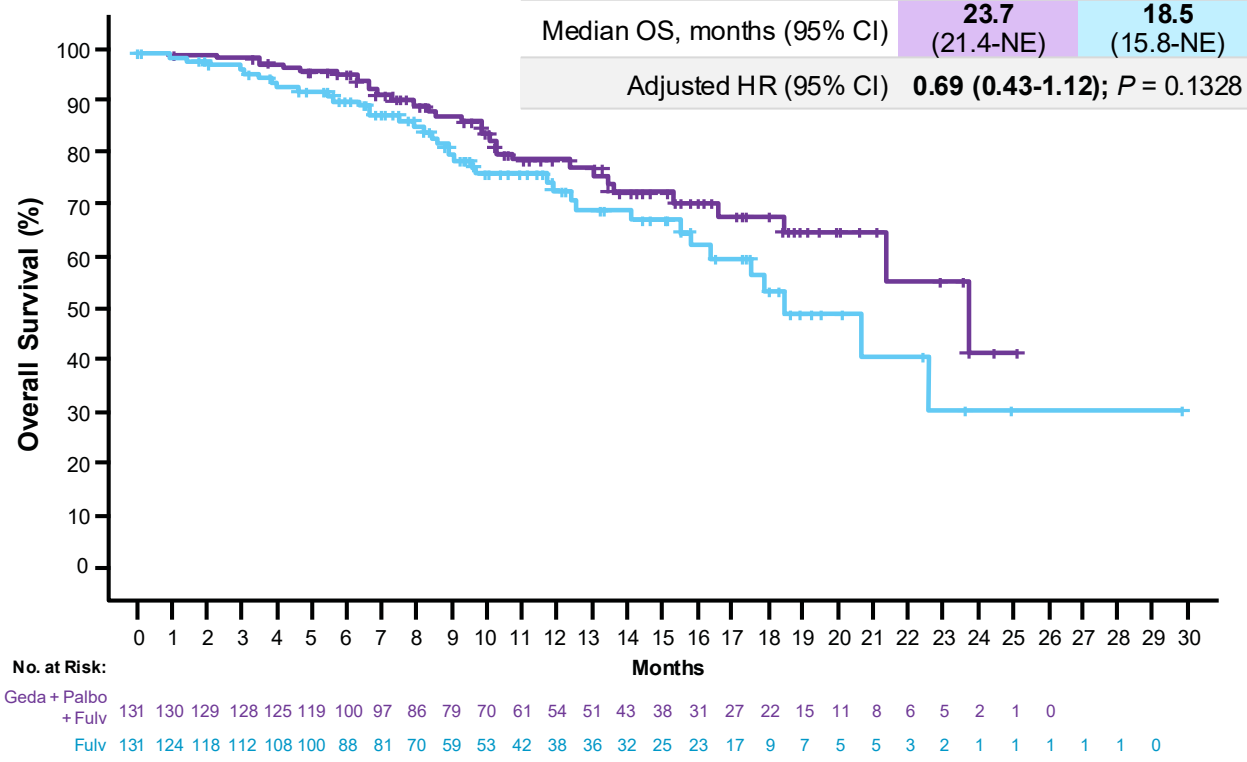
Geda + Fulv	130	126	93	89	64	63	45	44	33	33	22	22	17	16	11	8	6	5	5	3	1	1	1	1	1	1	0
Fulv	131	114	45	35	20	20	11	11	7	5	3	2	2	2	1	1	1	0									

Presenter: Sara A. Hurvitz, MD, FACP

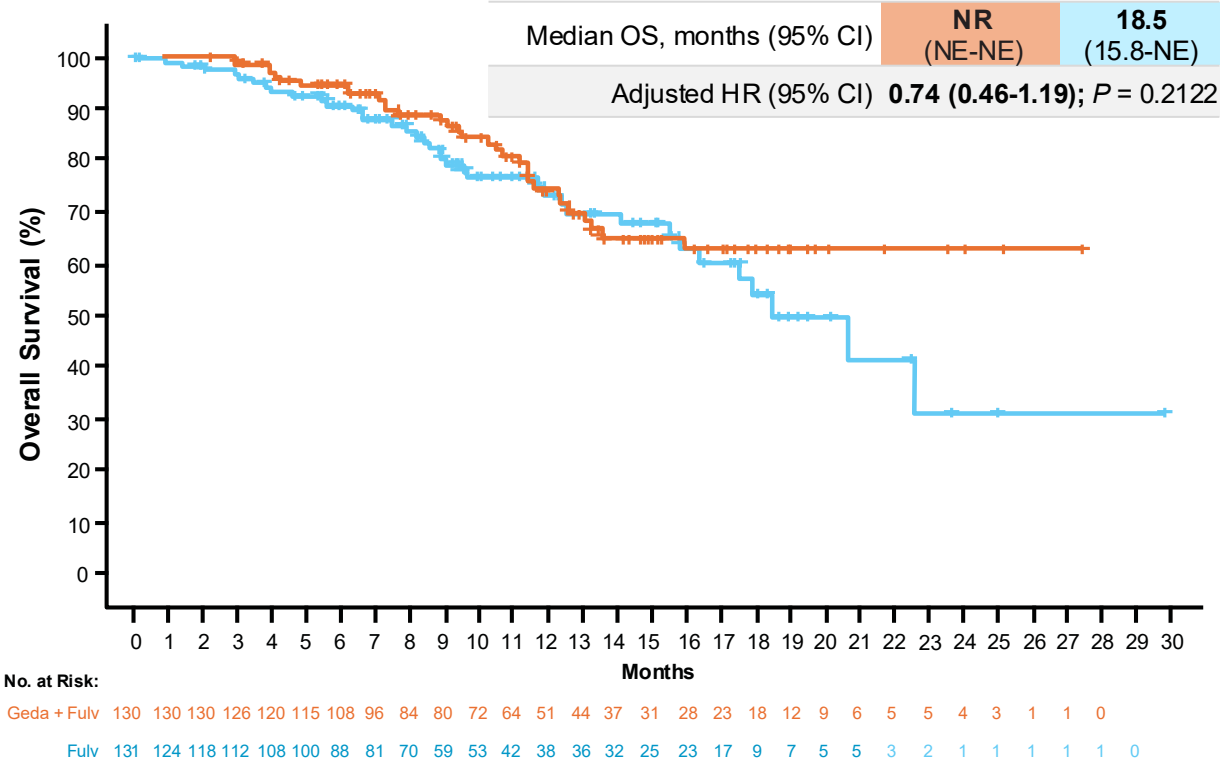
Hurvitz SA et al. *J Clin Oncol* 2026;44:1108-19.

Key Secondary Endpoint: Overall Survival (Interim Analysis)

	Geda + Palbo + Fulvestrant (n=131)	Fulvestrant (n=131)
Median OS, months (95% CI)	**23.7** (21.4-NE)	**18.5** (15.8-NE)
Adjusted HR (95% CI)	**0.69 (0.43-1.12)**; *P* = 0.1328	



	Geda + Fulvestrant (n=130)	Fulvestrant (n=131)
Median OS, months (95% CI)	**NR** (NE-NE)	**18.5** (15.8-NE)
Adjusted HR (95% CI)	**0.74 (0.46-1.19)**; *P* = 0.2122	



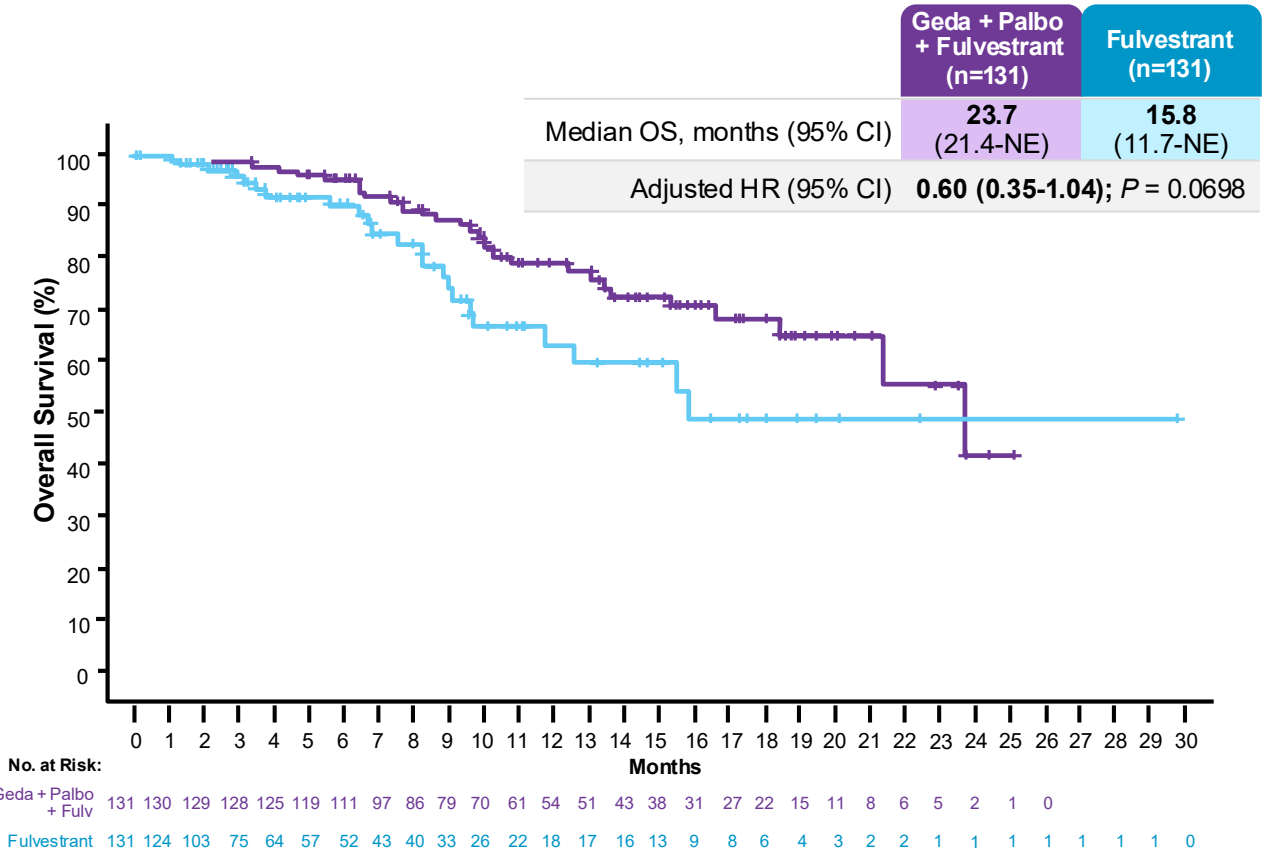
At data cutoff (30 May 2025):

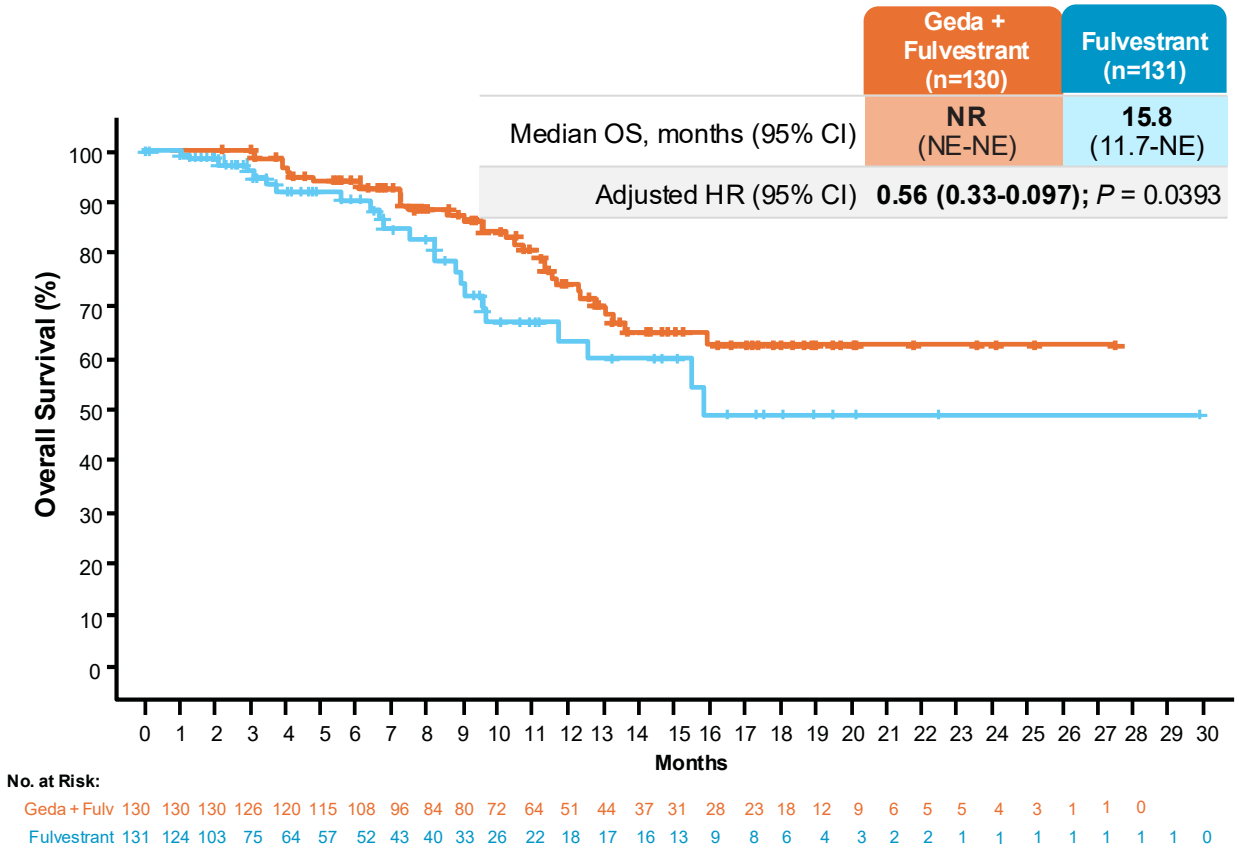
- 99 patients (25.3%) across arms died: gedatolisib triplet, n=30 (22.9%); gedatolisib doublet, n=32 (24.6%); fulvestrant, n=37 (28.2%)
- Represents 48% of the protocol-specified events for OS analysis
- Of 108 patients with disease progression on fulvestrant, 63 (58.3%) crossed over: geda triplet, n=52 (48.1%); geda doublet, n=11 (10.2%)

Presenter: Sara A. Hurvitz, MD, FACP

Hurvitz SA et al. *J Clin Oncol* 2026;44:1108-19.

Sensitivity Analysis: Interim OS Censored at Cross-Over





63 patients in the fulvestrant arm who crossed over to one of the gedatolisib regimens were censored in this sensitivity analysis

Presenter: Sara A. Hurvitz, MD, FACP

Hurvitz SA et al. *J Clin Oncol* 2026;44:1108-19.

Safety and Tolerability

Treatment-Related Adverse Events (Safety Population)*

SAE and discontinuation, n (%)	Gedatolisib + palbociclib + fulvestrant (n=130)			Gedatolisib + fulvestrant (n=130)			Fulvestrant (n=123)		
Pts with ≥1 SAE	14 (10.8)			12 (9.2)			1 (0.8)		
Study treatment D/C due to TRAE	3 (2.3)			4 (3.1)			0		
Deaths due to TRAE†	2 (1.5)			0			0		
Adverse events, n (%)	**Gedatolisib + palbociclib + fulvestrant (n=130)**			**Gedatolisib + fulvestrant (n=130)**			**Fulvestrant (n=123)**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Stomatitis‡	**90 (69.2)**	**25 (19.2)**	**0**	**74 (56.9)**	**16 (12.3)**	**0**	**0**	**0**	**0**
Neutropenia‡	85 (65.4)	68 (52.3)	13 (10.0)	2 (1.5)	0	1 (0.8)	1 (0.8)	1 (0.8)	0
Nausea	57 (43.8)	5 (3.8)	0	56 (43.1)	1 (0.8)	0	4 (3.3)	0	0
Rash‡	**36 (27.7)**	**6 (4.6)**	**0**	**42 (32.3)**	**7 (5.4)**	**0**	**0**	**0**	**0**
Vomiting	36 (27.7)	2 (1.5)	0	30 (23.1)	0	0	1 (0.8)	0	0
Fatigue	29 (22.3)	2 (1.5)	0	27 (20.8)	1 (0.8)	0	5 (4.1)	0	0
Diarrhea§	**22 (16.9)**	**2 (1.5)**	**0**	**16 (12.3)**	**1 (0.8)**	**0**	**0**	**0**	**0**
Hyperglycemia‡,§	**12 (9.2)**	**3 (2.3)**	**0**	**15 (11.5)**	**3 (2.3)**	**0**	**0**	**0**	**0**

Abbreviations: D/C, discontinued; Pts, patients; SAE, serious adverse event; TRAE, treatment-related adverse event (per investigator)
*Shown are adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted
†Grade 5 events include one considered related to palbociclib (pneumonia) and one due to hepatic failure in a patient with multiple liver metastasis considered related to all three drugs (and likely associated with disease)
‡For stomatitis, neutropenia, rash, and hyperglycemia, combined preferred terms shown; if a patient experienced multiple terms, it was counted once for the highest grade.
§Additional events of clinical importance

Presenter: Sara A. Hurvitz, MD, FACP

Hurvitz SA et al. *J Clin Oncol* 2026;44:1108-19.

Inhibiting the PI3K/AKT/mTOR Pathway: Key Messages

- *PIK3CA, AKT, PTEN* are mutated in ~ 40%, 10% and 10% of HR+ MBC and drive resistance to therapy
- Everolimus + exemestane, alpelisib + fulvestrant (for *PIK3CA*m) and capivasertib + fulvestrant (for *PIK3CA/AKT/PTEN*-altered) are approved for HR-positive MBC
- Future indication post-CDK4/6i: Gedatolisib plus fulvestrant, with or without palbociclib, for HR+, HER2-, *PIK3CA*-WT MBC

QUESTIONS?

Module 11: Colorectal Cancer (CRC)

Current and Future Role of Immune Checkpoint Inhibition in the Management of CRC — Dr Ciombor

Other Recent Advances in CRC Management — Dr Strickler

Faculty

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Research To Practice
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Duke University
Durham, North Carolina

Co-Moderator
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Module 11: Colorectal Cancer (CRC)

Current and Future Role of Immune Checkpoint Inhibition in the Management of CRC — Dr Ciombor

Other Recent Advances in CRC Management — Dr Strickler

Module 11: Colorectal Cancer

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Current and Future Role of Immune Checkpoint Inhibition in the Management of Colorectal Cancer

Kristen K. Ciombor, MD, MSCI
Associate Professor of Medicine, Vanderbilt University Medical Center
Ingram Associate Professor of Cancer Research, VICC
Co-Leader, VICC Gastrointestinal Oncology Research Program
Leader, Vanderbilt Health GI Oncology Section

April 26, 2026

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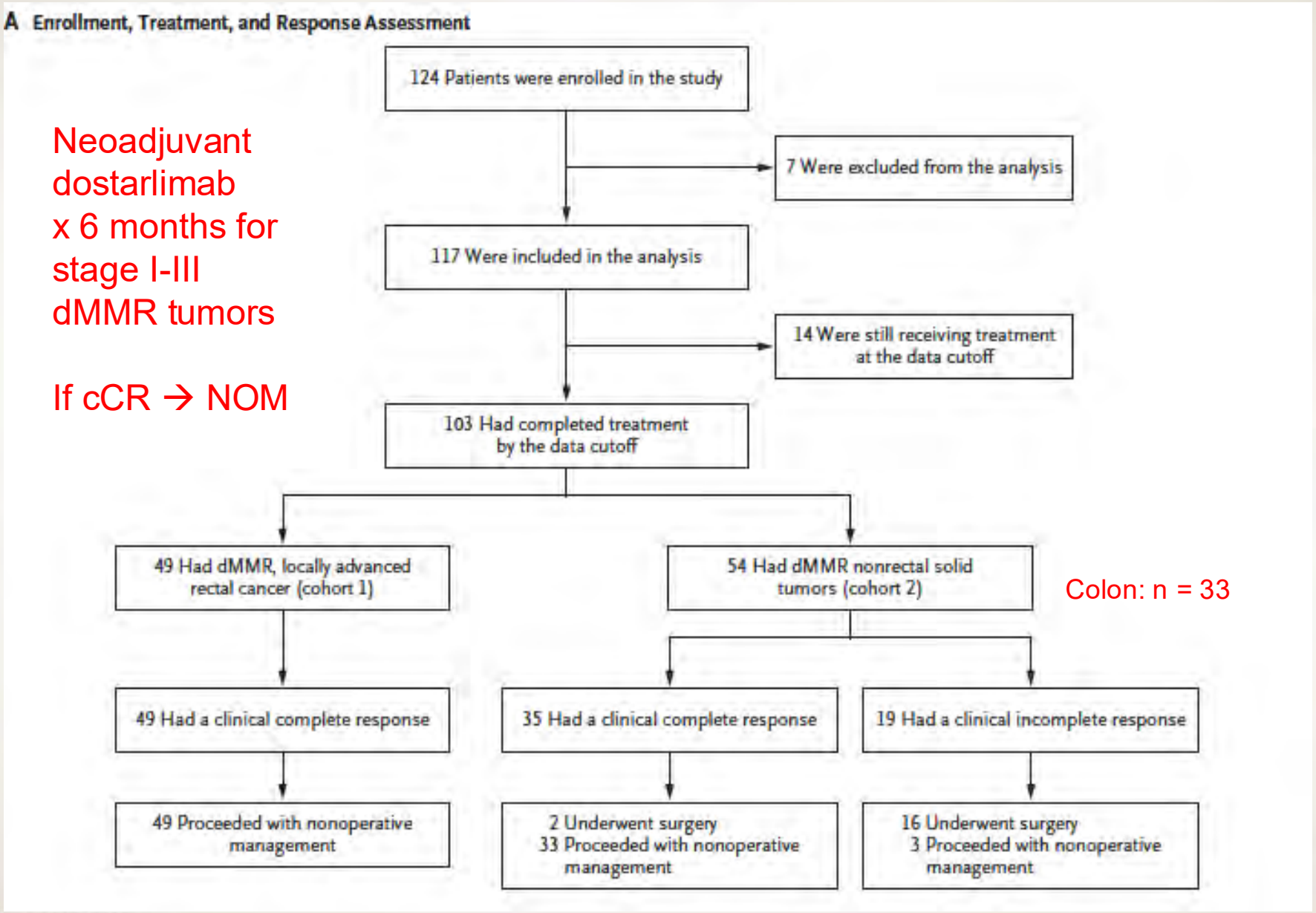
Disclosures

Advisory Committees	AbbVie Inc, Agenus Inc, ALX Oncology, BeOne, Bristol Myers Squibb, Exact Sciences Corporation, Exelixis Inc, Merck, Pfizer Inc, Summit Therapeutics, Taiho Oncology Inc, Tempus
Contracted Research	Array BioPharma Inc, a subsidiary of Pfizer Inc, Biomea Fusion Inc, Bristol Myers Squibb, Calithera Biosciences, Genentech, a member of the Roche Group, Incyte Corporation, Merck, NuCana, Pfizer Inc, Seagen Inc, Syndax Pharmaceuticals

Phase II Study of NOM of dMMR Tumors

Neoadjuvant
dostarlimab
x 6 months for
stage I-III
dMMR tumors

If cCR → NOM



Colon: n = 33

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Cercek A. *N Engl J Med.* 2025;392(23):2297-2308

Phase II Study of NOM of dMMR Tumors

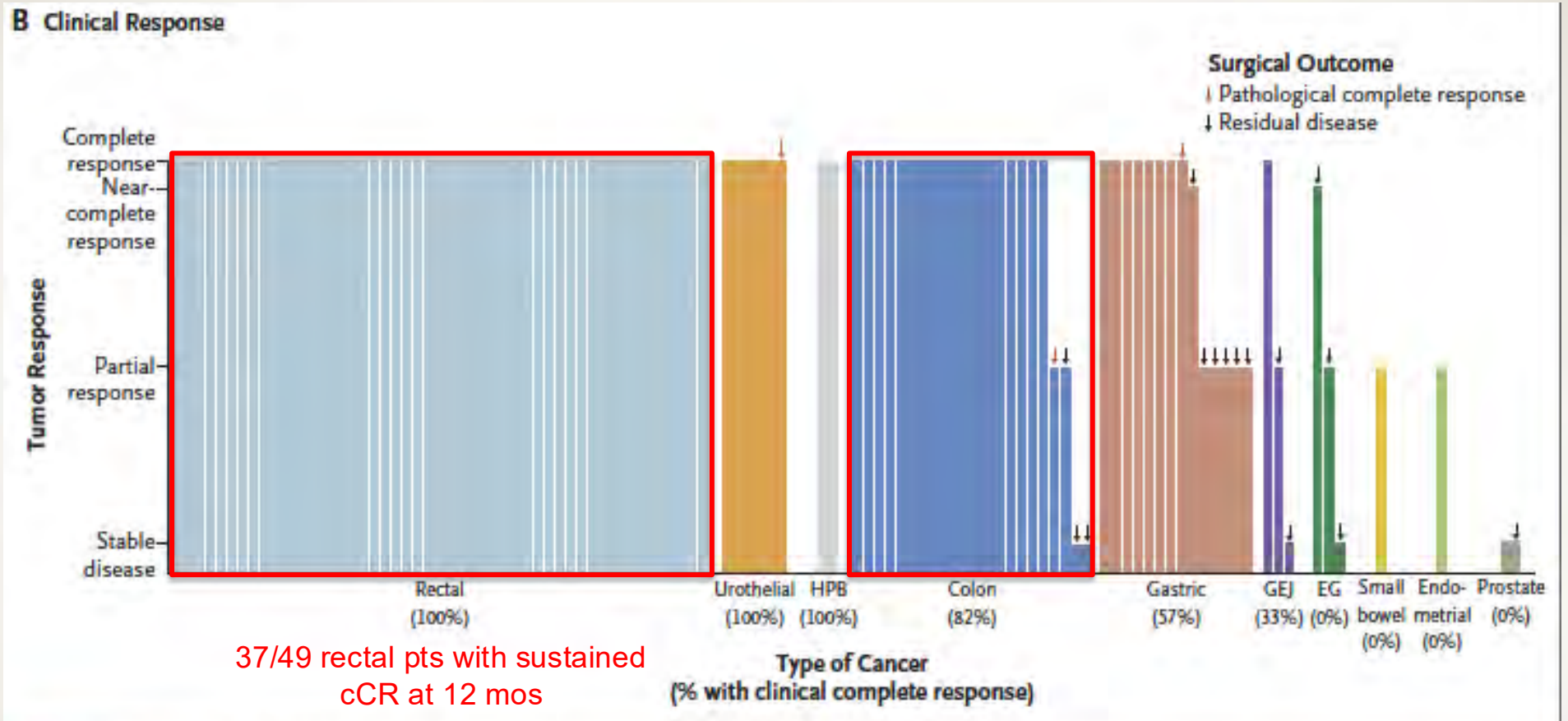

Figure 1. Enrollment, Treatment, and Response Assessment.

Panel A shows the distribution of patients after enrollment, treatment, and response assessment. Panel B shows the clinical response for each patient according to tumor type. Hepatobiliary (HPB) cancers consist of periampullary cancer and cholangiocarcinoma. EG denotes esophageal and GEJ gastroesophageal junction.

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Cercek A. *N Engl J Med.* 2025;392(23):2297-2308

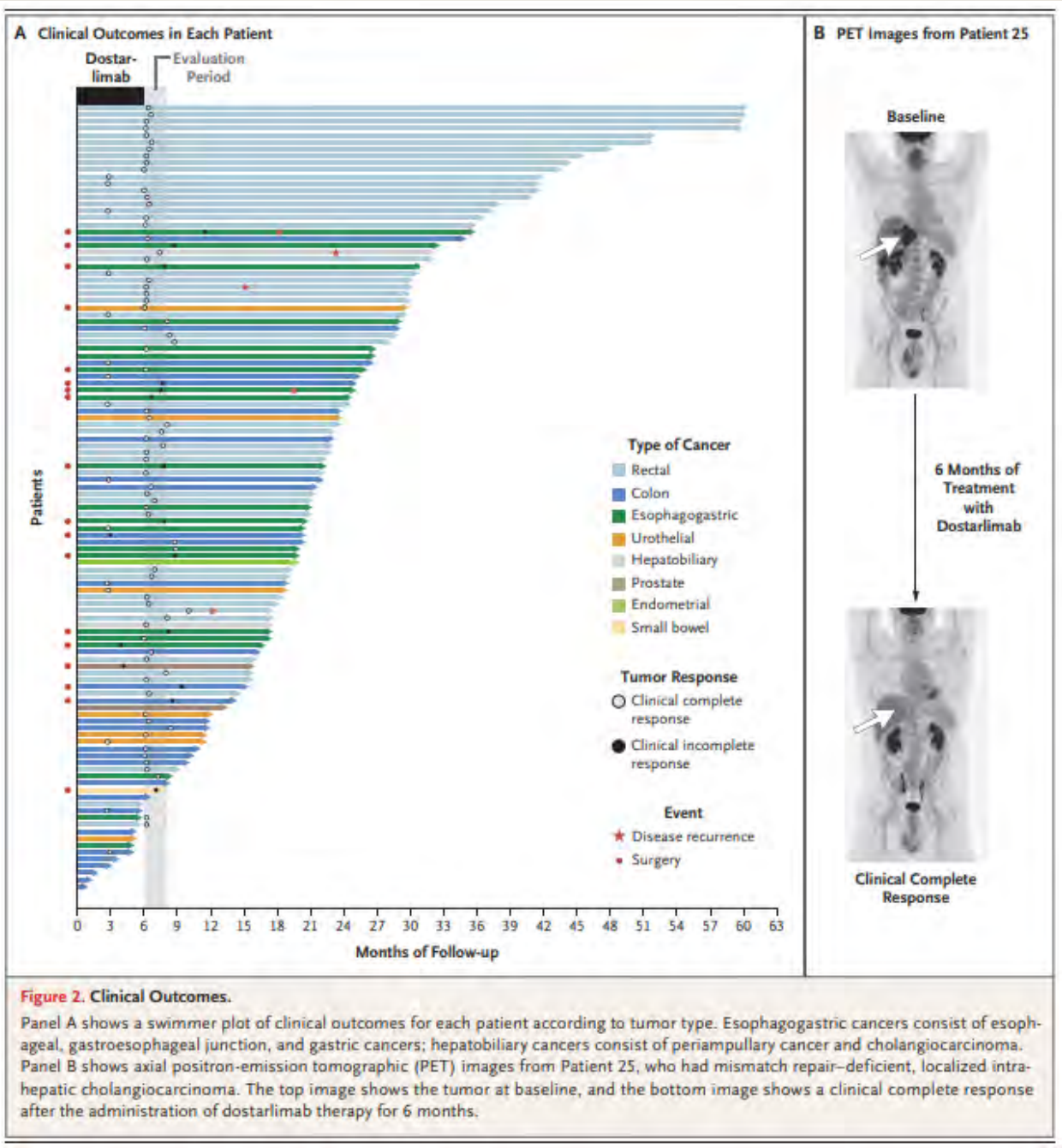

Figure 2. Clinical Outcomes.

Panel A shows a swimmer plot of clinical outcomes for each patient according to tumor type. Esophagogastric cancers consist of esophageal, gastroesophageal junction, and gastric cancers; hepatobiliary cancers consist of periampullary cancer and cholangiocarcinoma. Panel B shows axial positron-emission tomographic (PET) images from Patient 25, who had mismatch repair–deficient, localized intrahepatic cholangiocarcinoma. The top image shows the tumor at baseline, and the bottom image shows a clinical complete response after the administration of dostarlimab therapy for 6 months.

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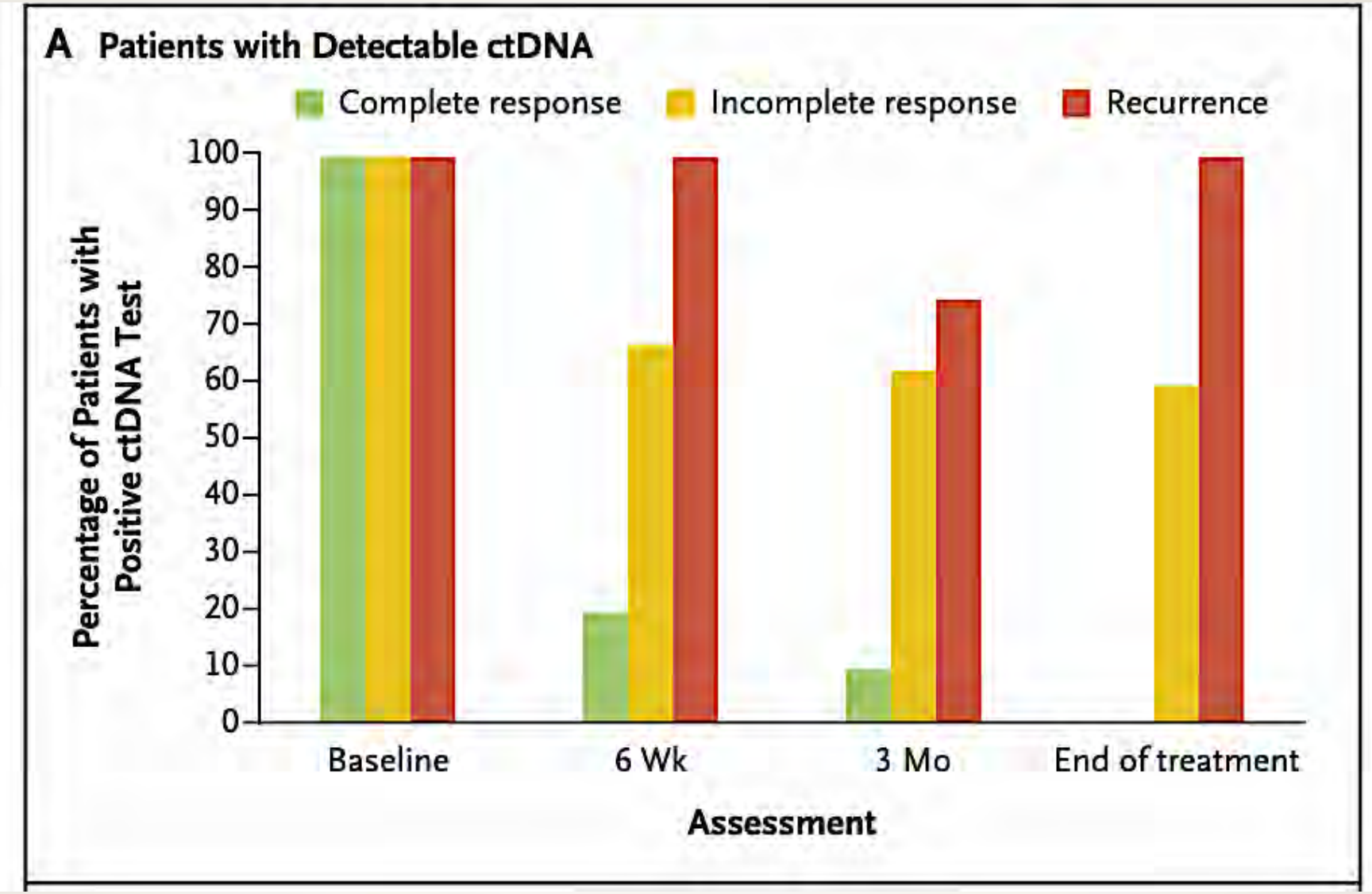
Cercek A. *N Engl J Med.* 2025;392(23):2297-2308



Cercek A. *N Engl J Med.* 2025;392(23):2297-2308

AZUR-1: Global, Multicenter, Single-Arm, Open-Label, Non-Randomized Phase 2 Study of Dostarlimab Monotherapy in Patients with MSI-H/dMMR LARC

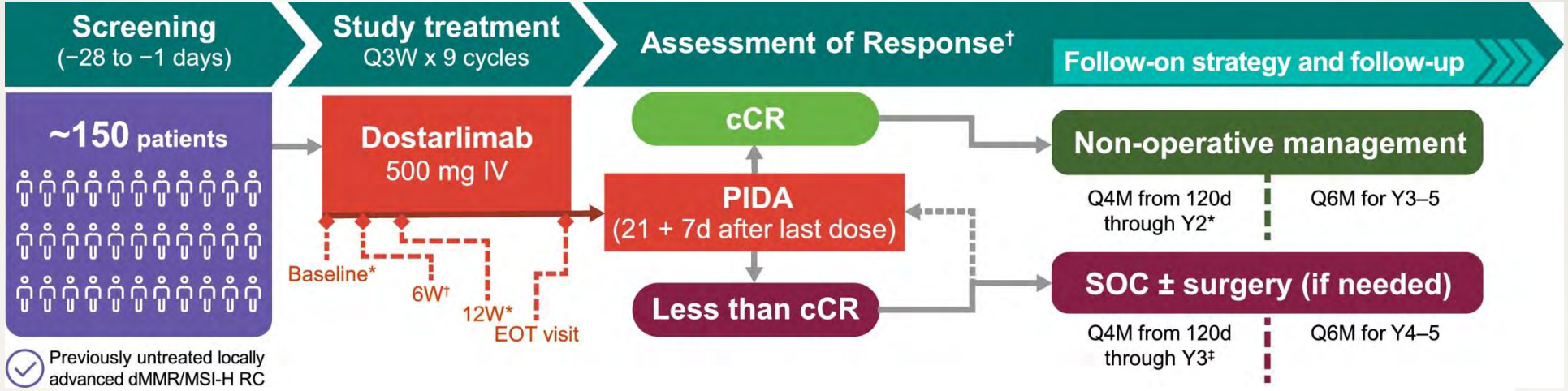


Figure 1 Study schema. When necessary, noncontrast-enhanced CT of the chest in combination with contrast-enhanced MRI of the abdomen/pelvis can be substituted for contrast-enhanced CT CAP. cCR = complete clinical response; CT = computed tomography; CT CAP = computed tomography scans of the chest, abdomen, and pelvis; d = day(s); dMMR = mismatch repair deficient; EFS_3 = 3-year event-free survival; EOT = end of treatment; IV = intravenous; MRI = magnetic resonance imaging; MSI-H = microsatellite instability high; PIDA = postintervention disease assessment; Q*n*M = every *n* months; Q*n*W = every *n* weeks; RC = rectal cancers; SOC = standard of care; W = weeks; Y = Year. *Disease assessments (CT CAP, rectal MRI, endoscopy, biopsy [when applicable]). †Disease assessments (endoscopy only). ‡EFS_3 through Y_3 (CT CAP, rectal MRI, endoscopy, biopsy [when applicable]).

- **Primary endpoint**: cCR by central review at 12 months
- **Key secondary endpoints**: cCR by central review at 24 and 36 mos, 3-year EFS

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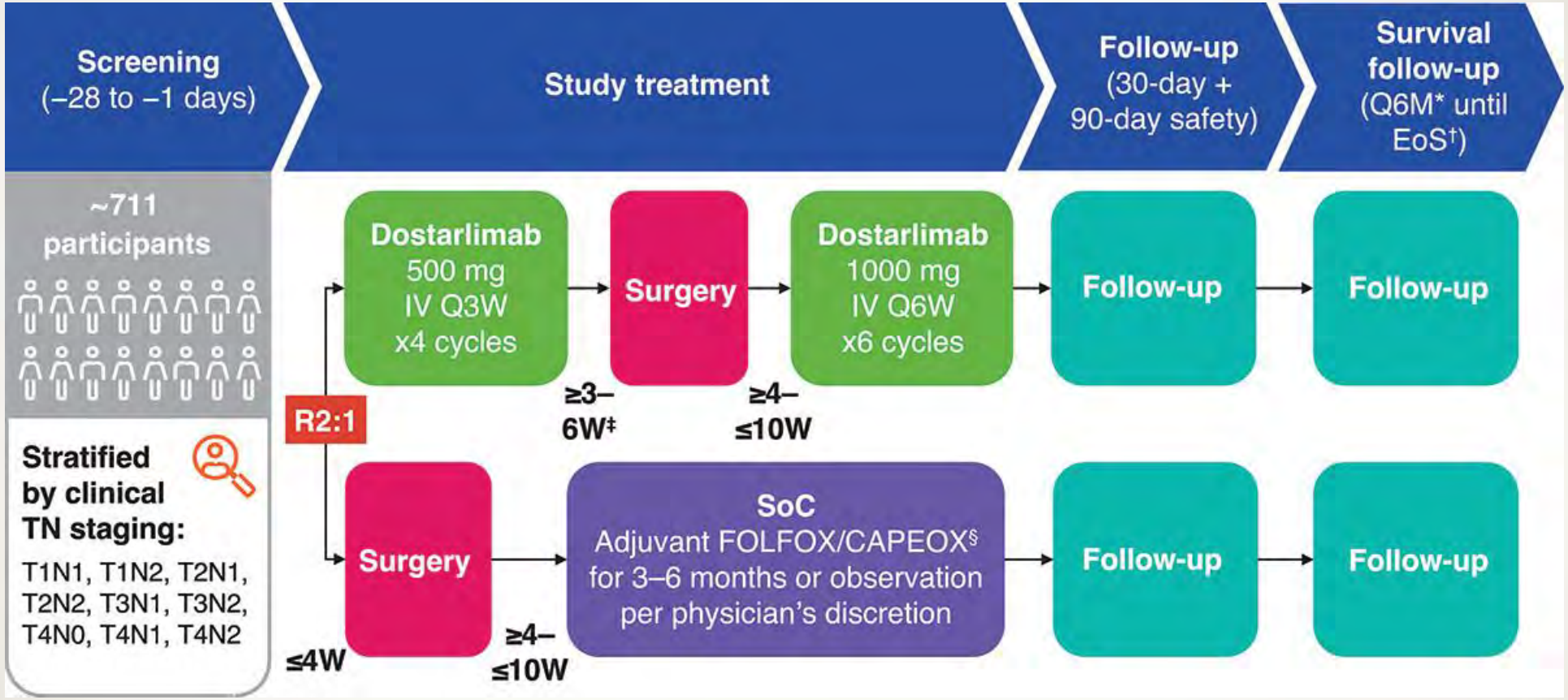
Cercek A, et al, 24(2): 325-330, *Clinical Colorectal Cancer*, 2025

AZUR-2: A Phase 3 Open-Label, Randomized Study of Perioperative Dostarlimab Monotherapy vs. SOC in Pts with T4N0 or Stage III MSI-H/dMMR Resectable Colon Cancer



- **Primary endpoint**: EFS
- **Key secondary endpoint**: OS

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Starling N et al. 22:137-145, *Future Oncology*, 2026

AZUR-4: Testing Neoadjuvant Dostarlimab Plus CAPEOX in pMMR/MSS Resectable Colon Cancer

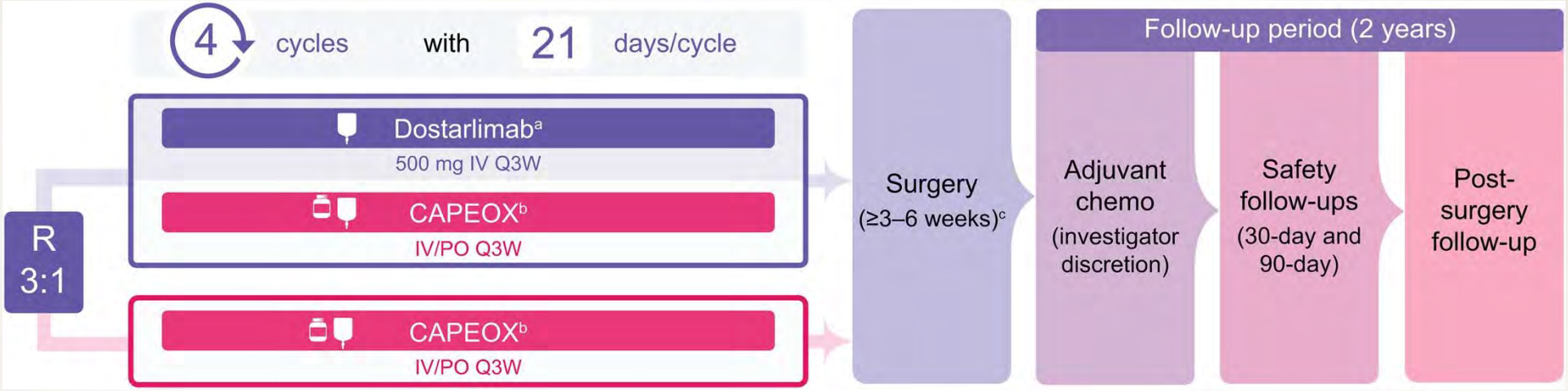

Figure 1 Study schema. [a]Dostarlimab solution for infusion will be administered as 500 mg Q3W dose beginning on day 1 of each 21-day cycle for 4 cycles. [b]Oxaliplatin will be administered as an infusion with dose of 130 mg/m² Q3W on day 1 of each 21-day cycle for 4 cycles. Capecitabine will be administered as an oral agent with twice-daily dosing of 1000 mg/m² for 14 days of a 21-day cycle for 4 cycles. [c]At least 3 and no more than 6 weeks after the last dose of neoadjuvant treatment. CAPEOX, capecitabine-oxaliplatin; IV, intravenously; PO, orally; Q3W, every 3 weeks; R, randomization.

- **Primary endpoints**: major pathological response, safety
- **Secondary endpoints**: feasibility, path response, ability to get to surgery

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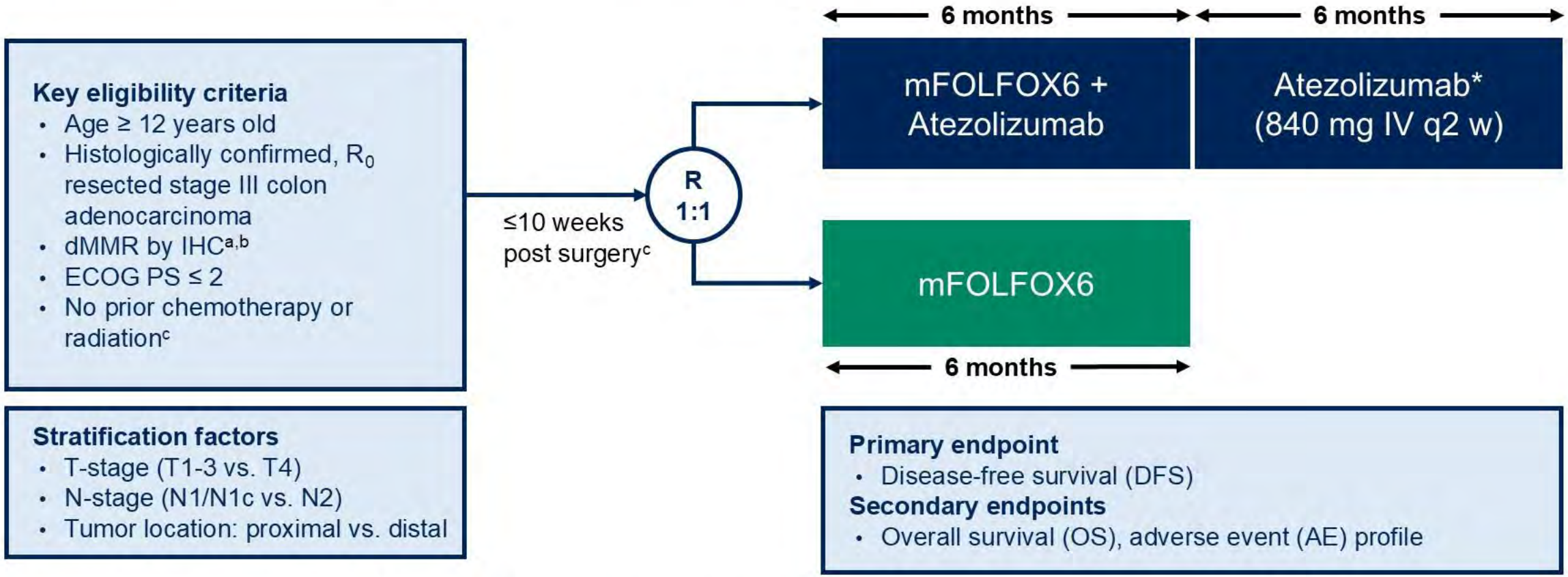
Rasschaert G, et al. *Clinical Colorectal Cancer*, 2026

Study Design

ATOMIC is a randomized, multicenter, open label phase 3 study



[a] **dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.**
[b] Lynch syndrome included.
[c] One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

Baseline Characteristics

	mFOLFOX6 + Atezo (N=355)	mFOLFOX6 (N=357)
Age (years)		
Median	65	63
Q1, Q3	51.0, 73.0	48.0, 73.0
Sex, n (%)		
Female	186 (52.4%)	206 (57.7%)
Male	169 (47.6%)	151 (42.3%)
Race, n (%)		
White	302 (85.1%)	305 (85.4%)
Black	28 (7.9%)	22 (6.2%)
Other	25 (6.0%)	30 (8.4%)
Primary Tumor Site, n (%)		
Proximal	301 (84.8%)	296 (82.9%)
Distal	53 (14.9%)	57 (16.0%)
Multiple	1 (0.3%)	4 (1.1%)

	mFOLFOX6 + Atezo (N=355)	mFOLFOX6 (N=357)
T-Stage, n (%)		
Tx	0	1 (0.3%)
T1	11 (3.1%)	4 (1.1%)
T2	30 (8.5%)	22 (6.2%)
T3	202 (56.9%)	216 (60.5%)
T4	112 (31.5%)	114 (31.9%)
N-Stage, n (%)		
N1/N1c	226 (63.7%)	225 (63.0%)
N2	129 (36.3%)	132 (37.0%)
Risk Group, n (%)		
Low (Tx-T3 and N1/N1c)	164 (46.2%)	164 (45.9%)
High (T4 and/or N2)	191 (53.8%)	193 (54.1%)
ECOG, n (%)		
0	238 (67.0%)	225 (63.0%)
1	111 (31.3%)	127 (35.6%)
2	6 (1.7%)	5 (1.4%)

Baseline patient characteristics were well balanced between study arms

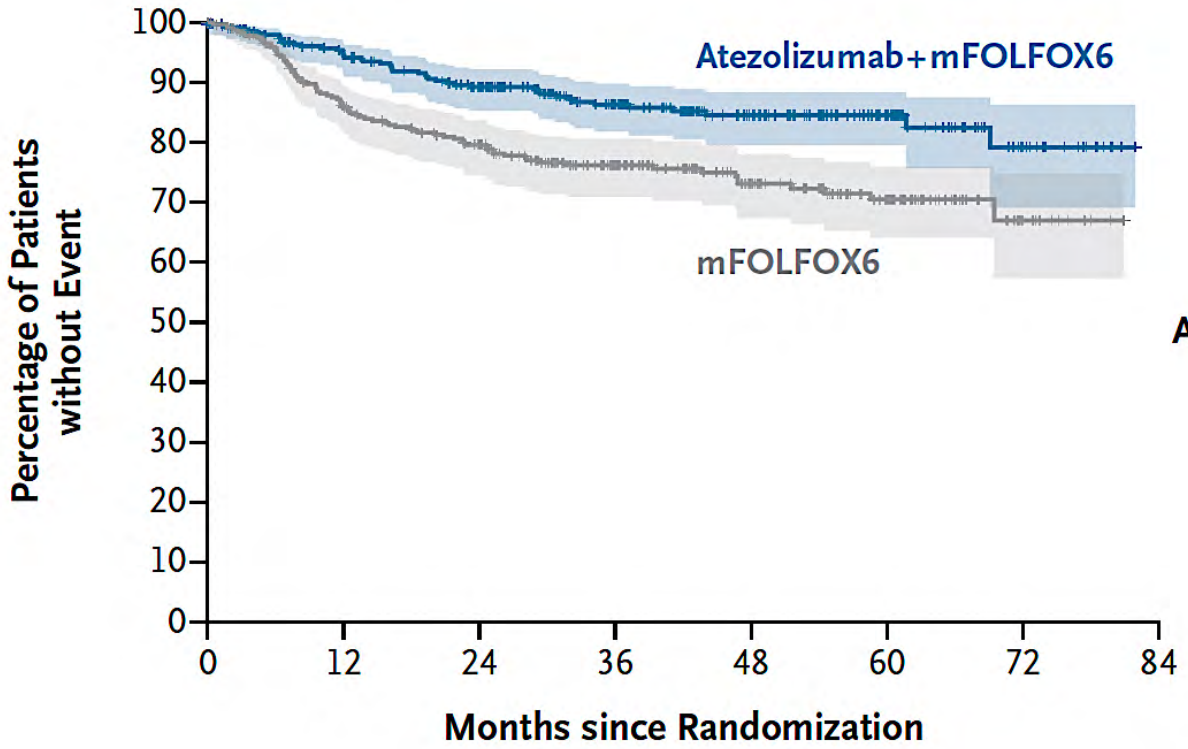
Sinicrope FA et al. N Engl J Med 2026;394:1155-66.

Treatment Exposure

	mFOLFOX6 + Atezo (N=346)#	mFOLFOX6 (N=334)#
Median treatment duration	5.5 months (mFOLFOX6); 10.9 months (Atezo)	5.4 months
Fluorouracil Bolus, N	**344**	**331**
Median cycles, n (range)	12 (1, 13)	12 (1, 12)
Median % dose received (range)	84.5 (8.0, 104.9)	85.7 (8.0, 103.9)
Fluorouracil Infusion, N	**345**	**333**
Median cycles, n (range)	12 (1, 13)	12 (1, 12)
Median % dose received (range)	85.4 (8.2, 105.2)	88.0 (8.2, 104.7)
Oxaliplatin, N	**346**	**334**
Median cycles, n (range)	10 (1, 13)	10 (1, 12)
Median % dose received (range)	71.0 (8.2, 105.6)	66.9 (8.2, 102.1)
Atezolizumab*, N	**346**	N/A
Median cycles, n (range)	23 (1, 26)	N/A
Median % dose received (range)	96 (4, 100)	N/A

Received at least one dose of treatment; 4 patients randomized to Atezo arm never received Atezo.
* No dose modification allowed.

Primary Endpoint: DFS



	No. of Events/ Total No. of Patients	3-Yr Disease-free Survival (95% CI)
		percent
Atezolizumab+mFOLFOX6	46/355	86.3 (81.8–89.8)
mFOLFOX6	81/357	76.2 (70.9–80.6)

Hazard ratio for disease recurrence or death, 0.50 (95% CI, 0.35–0.73)
Stratified P<0.001 by log-rank test

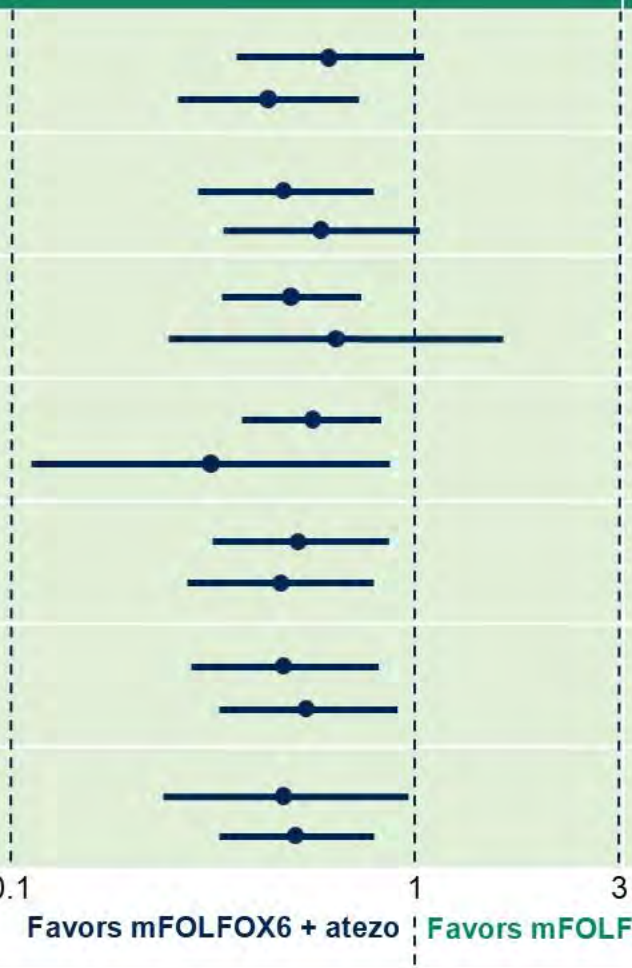
No. at Risk								
Atezolizumab+mFOLFOX6	355	296	259	181	112	59	17	0
mFOLFOX6	357	264	229	160	109	63	11	0

Median follow-up 40.9 mos

Sinicrope FA et al. N Engl J Med 2026;394:1155-66.

DFS by Subgroups

		mFOLFOX6 + Atezo	mFOLFOX6	HR (95% CI)
Age	< 65 year	22/173	36/187	0.61 (0.36, 1.04)
	≥ 65 year	23/182	44/170	0.43 (0.26, 0.72)
Sex	Female	24/186	50/206	0.48 (0.29, 0.77)
	Male	21/169	30/151	0.58 (0.33, 1.01)
Race	White	38/302	69/305	0.50 (0.33, 0.74)
	Other	7/53	11/52	0.63 (0.25, 1.63)
Tumor Location	Proximal	40/301	65/296	0.56 (0.38, 0.83)
	Distal	5/53	14/57	0.31 (0.11, 0.87)
T-Stage	Tx/T1-T3	23/243	44/243	0.51 (0.31, 0.85)
	T4	22/112	36/114	0.46 (0.27, 0.79)
N-Stage	$N1/N1_c$	21/226	41/225	0.48 (0.28, 0.81)
	N2	24/129	39/132	0.54 (0.33, 0.90)
Risk Group	Low*	12/164	25/164	0.47 (0.24, 0.94)
	High*	33/191	55/193	0.51 (0.33, 0.78)
		Events/Patients	Events/Patients	



*Low (Tx-T3 and N1/N1c); High (T4 or N2)

Safety Summary

Characteristics	mFOLFOX6 + Atezo (N=346)#	mFOLFOX6 (N=334)#
Any Grade AE, % (n)	100% (346)	95.1% (329)
Treatment-related	99.7% (345)	94.2% (326)
Grade 3-4 AE, % (n)	83.8% (290)	69.1% (239)
Treatment-related	72.3% (250)	59.2% (205)
Grade 5 AE, % (n)	1.7% (6)	0.6% (2)
Treatment-related	0.6% (2)*	0.0% (0)

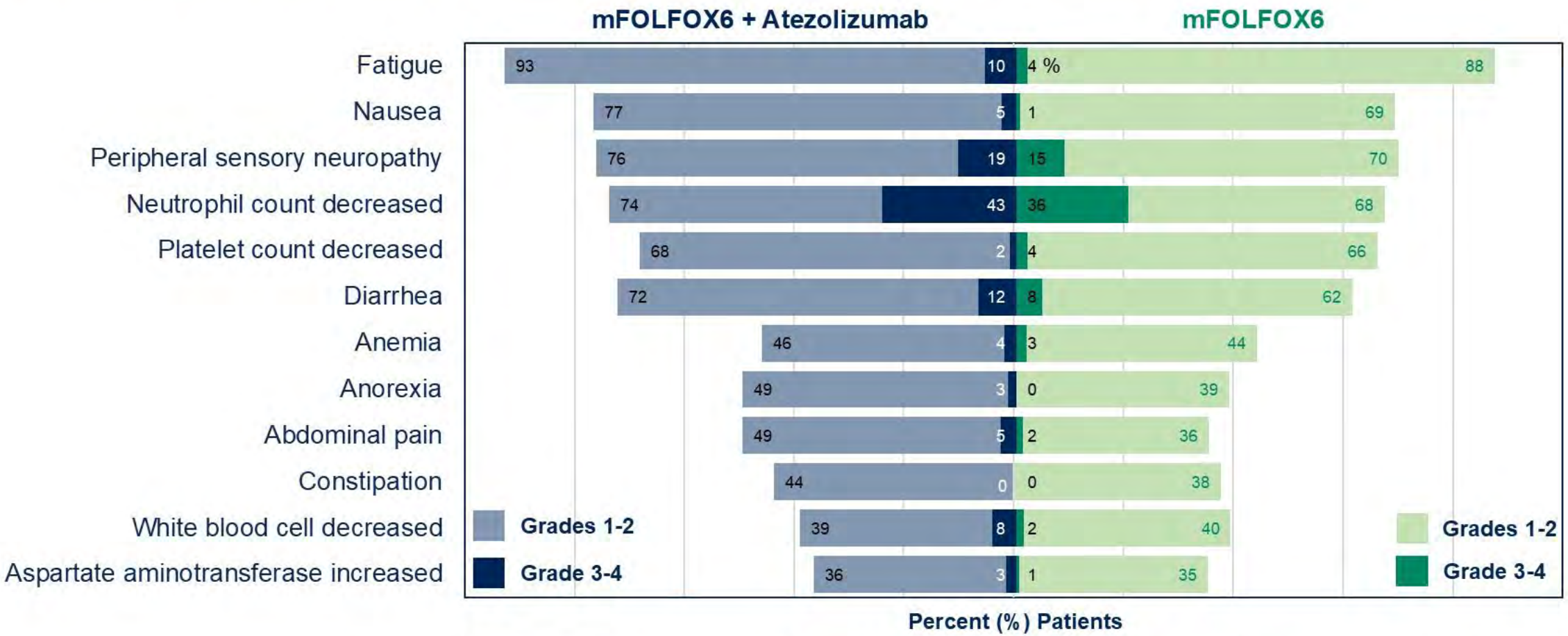
Investigator attribution of treatment-related adverse events (AE)

Received at least one dose of treatment

*1 sudden death NOS (possibly related); 1 sepsis (possibly related)

Patient Safety

AEs Occurring in > 35% of Evaluable* Patients



Neutrophil count decrease	mFOLFOX6 + Atezolizumab	mFOLFOX6
Grade 3, n (%)	100 (28.9%)	97 (29.0%)
Grade 4, n (%)	49 (14.2%)	23 (6.9%)

* Evaluable patients: received at least 1 treatment dose

Sinicrope FA et al. N Engl J Med 2026;394:1155-66.

From: Kapisthalam Kumar <kapimad@gmail.com>

Date: Saturday, April 18, 2026 at 2:30 PM

To: Dr Neil Love <drneillove@researchtopractice.com>

Subject: [EXTERNAL] INT case

Hi Neil

I wonder whether you will be able discuss this case in the upcoming meeting which I will be attending

60+ WF Stage II colon ca T4NoMo S/PR R0 resection

MSI high by IHC but negative germ line

BRAF mutated

Has some post op wound dehiscence 4x2cm not infected on wound vac

ct DNA negative

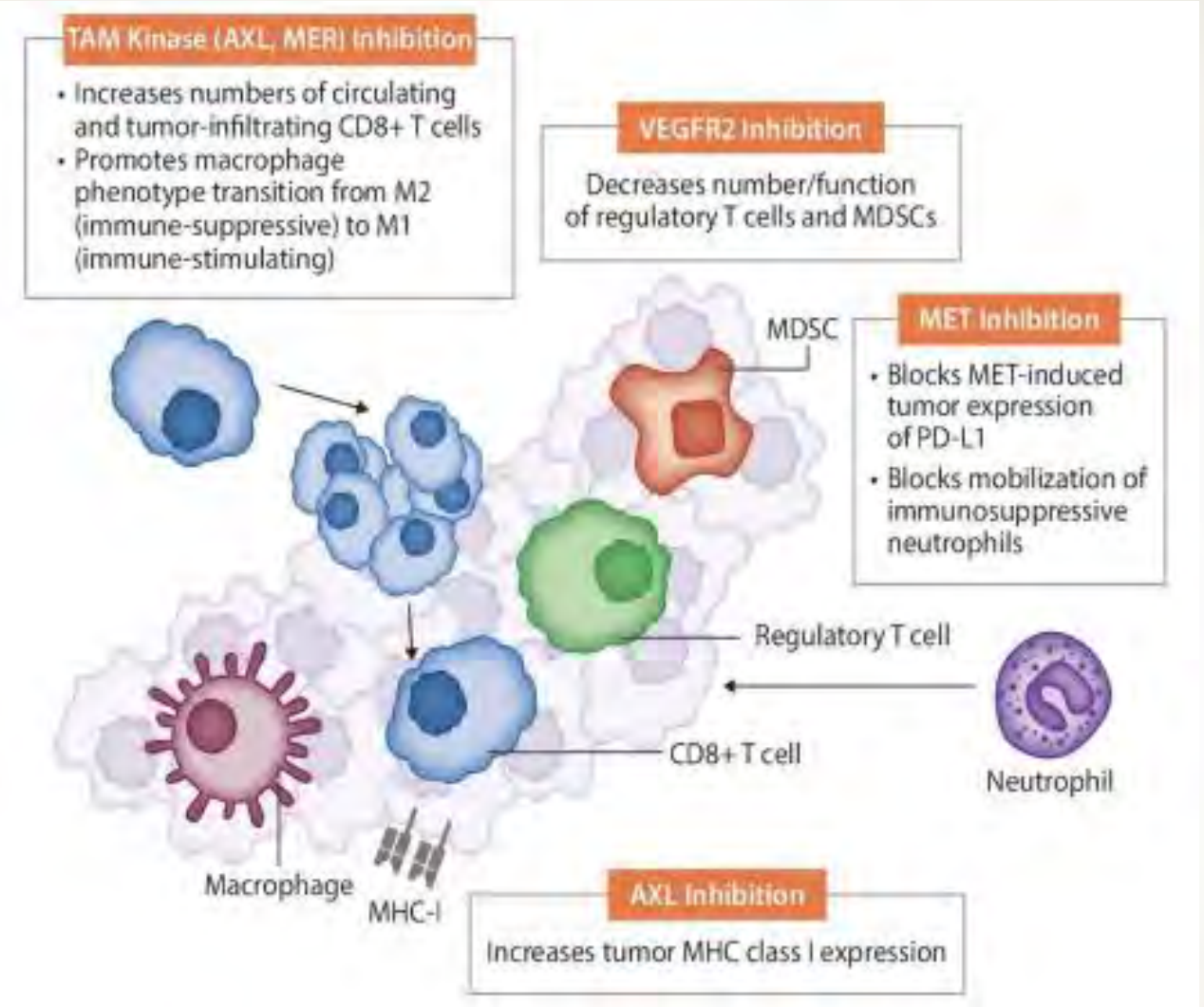
Should this pt get Chemotherapy FOLFOX OR CAPOX alone

Or should we treat like a stage 3 with chemo+ Atezo

Or is there a role for just immunotherapy

Thanks

Zanzalintinib Mechanism of Action



Regorafenib: VEGFR1/2/3, TIE2, PDGFR-α,-β, FGFR1/2, KIT, RET, RAF, BRAF
Fruquintinib: VEGFR1-3

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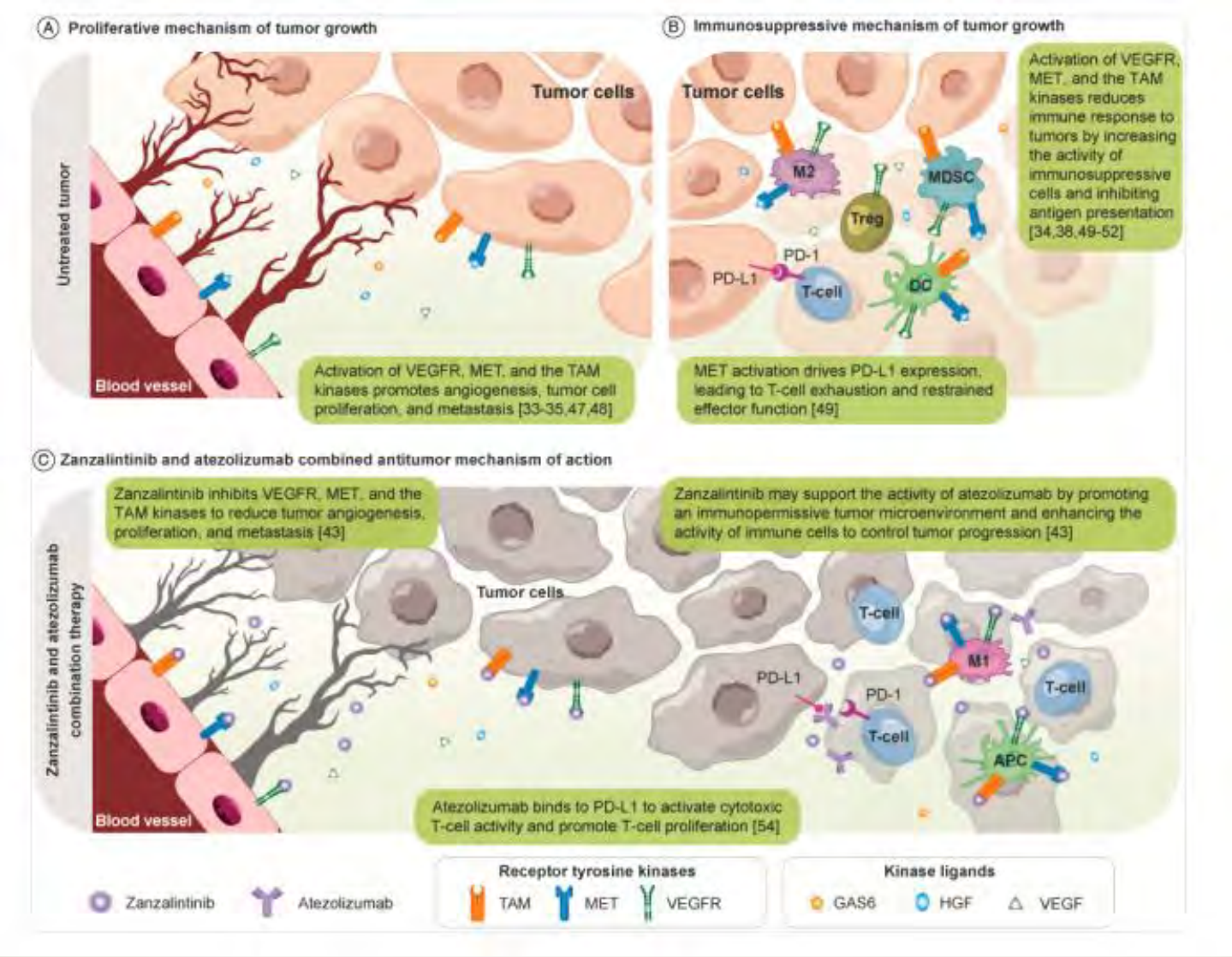
Elez E, ESMO 2025

Zanzalintinib + Atezolizumab: Rationale



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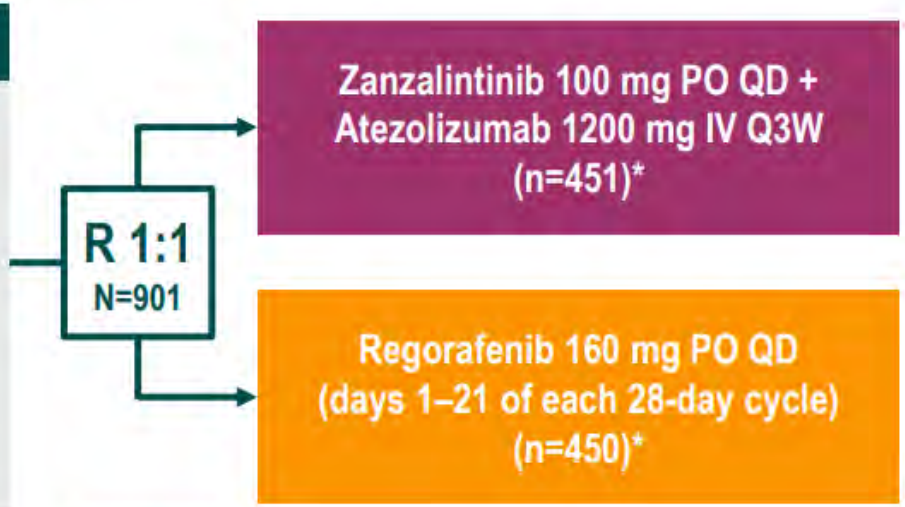
Saeed A, et al. 20(24):1733-1743, *Future Oncol*, 2024

STELLAR-303 (NCT05425940) Study Design

Patient Population

- Aged ≥18 years
- Documented to not have MSI-H or dMMR status
- mCRC that radiographically progressed on or was refractory or intolerant to prior standard-of-care therapy, which had to include all the following (if approved and available in the country where the patient is randomized):
  - Fluoropyrimidine, irinotecan and oxaliplatin ± anti-VEGF antibody
  - Anti-EGFR antibody (if *RAS* wild type)
  - BRAF inhibitor (if known *BRAF* V600E mutation)



Stratification Factors

- Geographic region (Asia/rest of the world)
- *RAS* status (wild type/mutant)
- Presence of liver metastases (yes/no)

Endpoints

Dual primary	OS in the ITT population OS in patients without liver metastases (nlmITT)
Key secondary	PFS,† ORR,† Safety‡

*Treatment beyond radiographic progression was allowed per Investigator discretion. †According to Response Evaluation Criteria In Solid Tumors version 1.1. Statistical significance cannot be claimed until superiority of OS in both the ITT and non-liver metastasis ITT populations has been demonstrated in the final analysis. ‡According to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; ITT, intention to treat; IV, intravenous; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; nlmITT, subset of patients without liver metastases; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral administration; Q3W, every 3 weeks; QD, once daily; VEGF, vascular endothelial growth factor.

Anwaar Saeed, MD

BERLIN 2025 ESMO congress

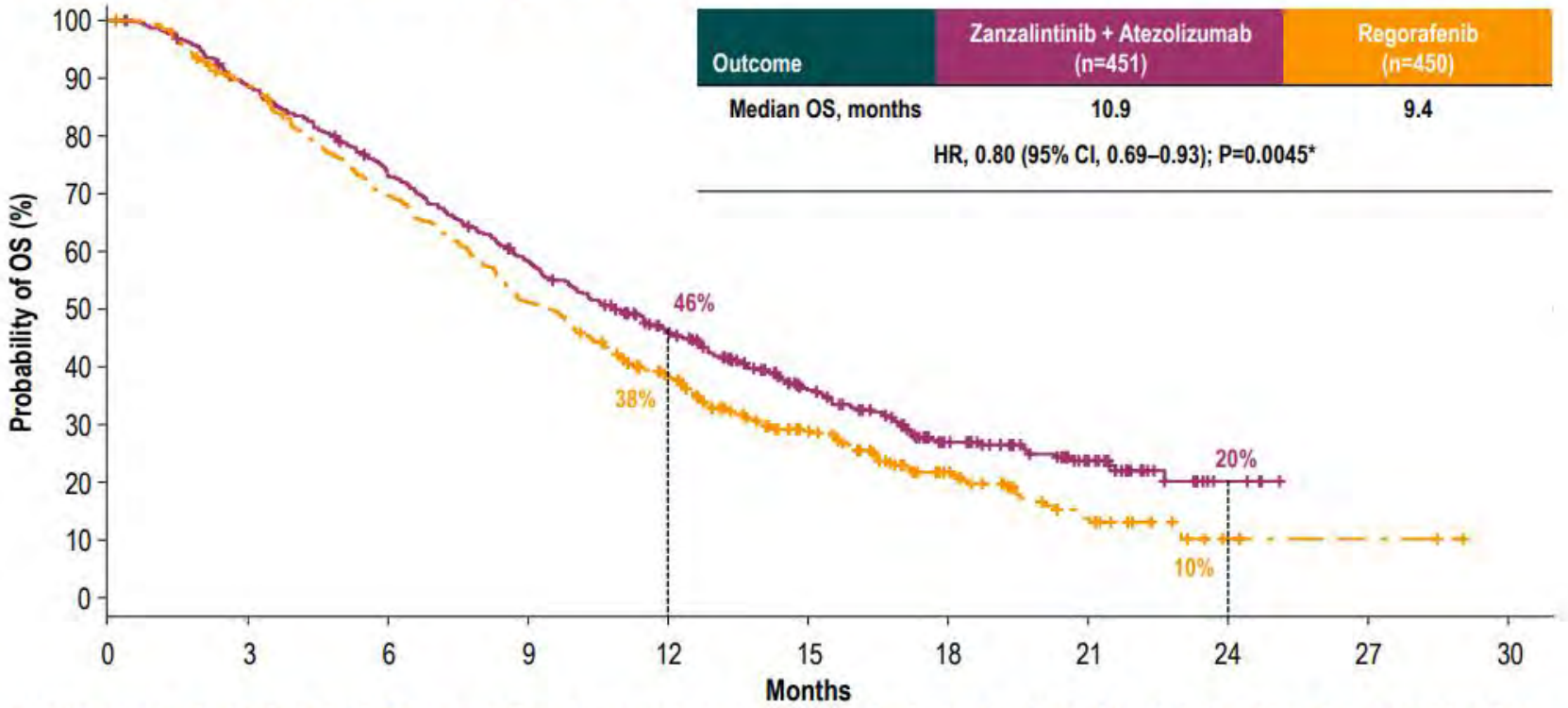
Baseline Characteristics (ITT Population)

Characteristic	Zanzalintinib + Atezolizumab (n=451)	Regorafenib (n=450)
Age, median (range), years	60 (29–84)	60 (29–85)
<65 / ≥65 years, %	65 / 35	67 / 33
Sex, Male / Female, %	58 / 42	60 / 40
Geographic region, Asia / Rest of the world, %	35 / 65	35 / 65
Race, White / Asian / Black / Other / Not reported, %	55 / 36 / 2 / 3 / 3	53 / 39 / 2 / 2 / 5
ECOG performance status score, 0 / 1, %	47 / 53	44 / 55
Location of the primary tumor, Rectum / Colon (left side vs right side*), %	37 / 63 (41 vs 22)	34 / 66 (41 vs 24)
Time to randomization since initial mCRC diagnosis, median (range), years	2.5 (0–14)	2.3 (0–15)
< 18 / ≥ 18 months, %	19 / 81	24 / 76
Presence of liver metastasis, Yes / No, %	59 / 41	56 / 44
***RAS* status,** Wild type / Mutant, %	41 / 59	40 / 60
***BRAF* status,** Wild type / Mutant / not tested, %	75 / 3 / 22	78 / 4 / 19
Prior systemic therapies for mCRC, %		
Prior fluoropyrimidine, irinotecan, and oxaliplatin	>99†	100
Any prior anti-VEGF antibody	80	83
Any prior anti-EGFR antibody	41	42

*Right side includes the transverse colon. †Of the two patients who did not receive all three agents, one received a fluoropyrimidine, oxaliplatin, and bevacizumab without having received irinotecan and the other received two fluoropyrimidines, irinotecan, bevacizumab, and cetuximab without having received oxaliplatin. ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ITT, intention to treat; mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor.

Anwaar Saeed, MD

OS Analysis (ITT Population)



Outcome	Zanzalintinib + Atezolizumab (n=451)	Regorafenib (n=450)
Median OS, months	10.9	9.4
HR, 0.80 (95% CI, 0.69–0.93); P=0.0045*		

- The interim analysis in the nImITT population (dual primary endpoint) showed a trend in OS favoring the combination (stratified HR, 0.79 [95% CI, 0.61–1.03; P=0.087]; median, 15.9 versus 12.7 months with regorafenib)

*Two-sided alpha = 0.015. CI, confidence interval; HR, hazard ratio; ITT, intention to treat; nImITT, subset of patients without liver metastases; OS, overall survival.

Anwaar Saeed, MD

Saeed A, ESMO 2025; Hecht JR, Lancet 2025.

OS Subgroup Analyses (ITT Population)—Key Subgroups

An OS benefit with zanzalintinib + atezolizumab vs regorafenib was consistently observed across key subgroups

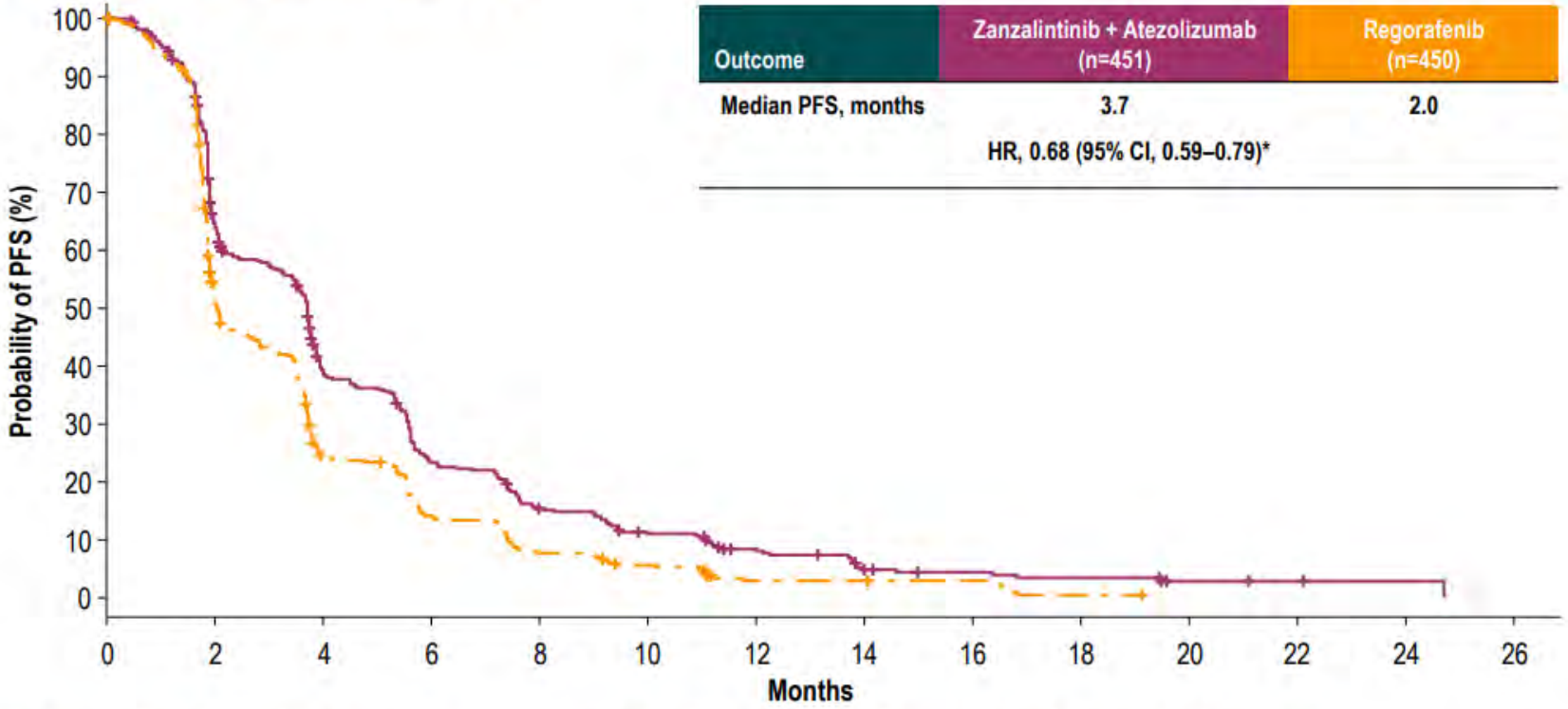
Subgroup	HR (95% CI)	Zanzalintinib + Atezolizumab median OS, months	Regorafenib median OS, months
Geographic region			
Asia	0.77 (0.59–1.00)	11.5	8.8
Rest of the world	0.82 (0.68–0.99)	10.9	9.8
***RAS* status**			
Wild type	0.79 (0.61–1.01)	12.0	10.4
Mutant	0.80 (0.66–0.98)	10.3	8.7
Liver metastases			
Yes	0.78 (0.65–0.94)	8.9	7.7
No	0.77 (0.59–1.01)	15.9	12.7
Prior anti-VEGF antibody treatment			
Yes	0.80 (0.68–0.95)	10.5	8.8
No	0.80 (0.56–1.15)	11.5	11.1

ITT, intention to treat; OS, overall survival; VEGF vascular endothelial growth factor.

Anwaar Saeed, MD

Saeed A, ESMO 2025; Hecht JR, Lancet 2025.

PFS (ITT Population)



Outcome	Zanzalintinib + Atezolizumab (n=451)	Regorafenib (n=450)
Median PFS, months	3.7	2.0
	HR, 0.68 (95% CI, 0.59–0.79)*	

- PFS for zanzalintinib + atezolizumab versus regorafenib was generally consistent across subgroups

*Statistical significance for PFS cannot be claimed at this analysis per the prespecified hierarchical testing strategy. ITT, intention to treat; PFS, progression-free survival.

Anwaar Saeed, MD

Saeed A, ESMO 2025; Hecht JR, Lancet 2025.

Best Overall Response (ITT Population)

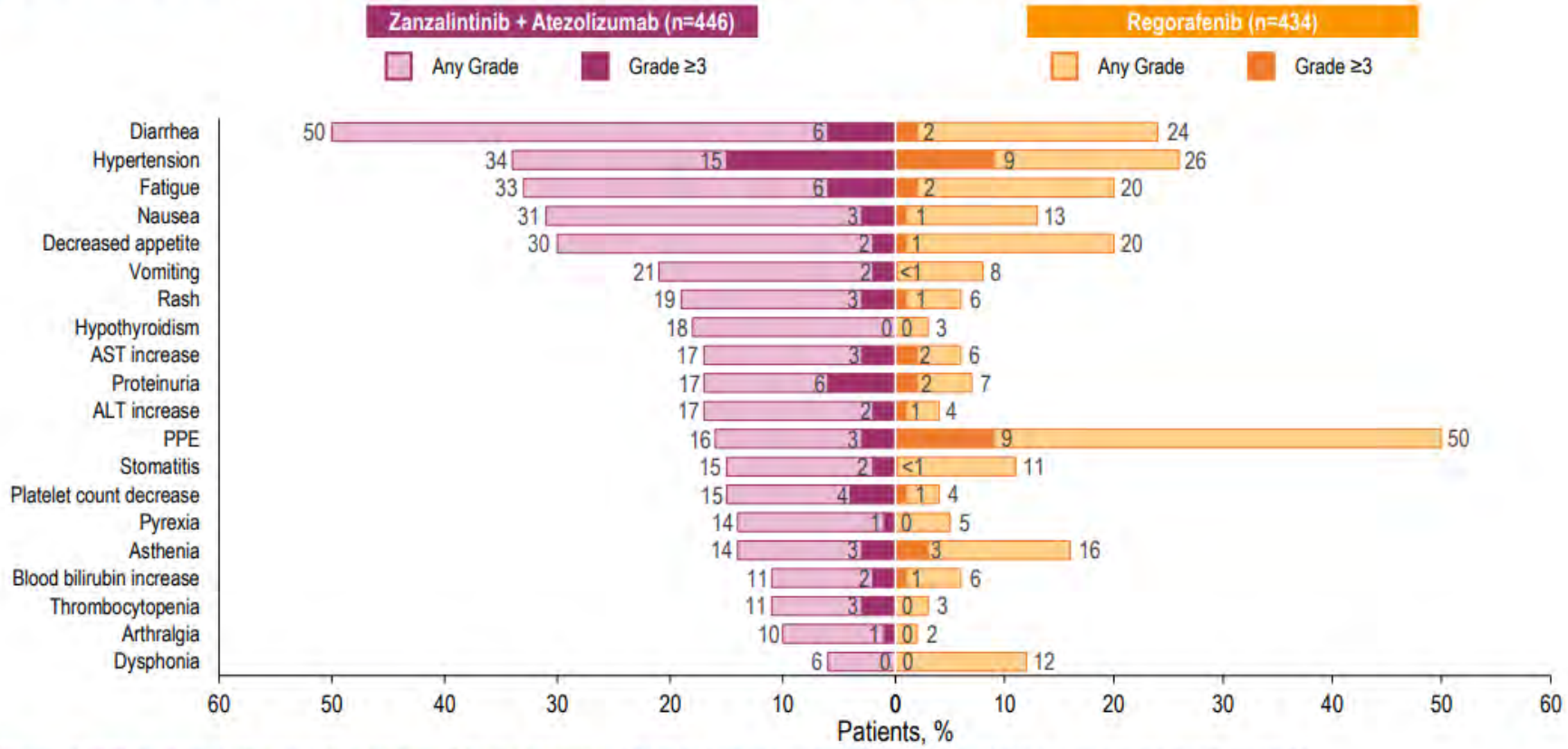
Response Outcome	Zanzalintinib + Atezolizumab (n=451)	Regorafenib (n=450)
Best overall response, n (%)*		
Complete response	0	0
Partial response	16 (4)	5 (1)
Stable disease	226 (50)	178 (40)
Progressive disease	156 (35)	216 (48)
Not evaluable	53 (12)	51 (11)
Objective response rate, n (%)	16 (4)	5 (1)
95% CI	(2–6)	(0–3)
Disease control rate, n (%)	242 (54)	183 (41)
95% CI	(49–58)	(36–45)

*Assessed based on Response Evaluation Criteria in Solid Tumors version 1.1 criteria. ITT, intention to treat.

Anwaar Saeed, MD

Saeed A, ESMO 2025; Hecht JR, Lancet 2025.

Summary of TRAEs* (Safety Population)



*Occurring in ≥10% of patients in either group; preferred terms of disease progression under study in adverse event database, as per medical review, are excluded. Events are listed by decreasing frequency in the any grade zanzalintinib + atezolizumab group. Adverse events are classified according to the Medical Dictionary for Regulatory Activities, version 28.0. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia syndrome; TRAE, treatment-related adverse event.

Anwaar Saeed, MD

Saeed A, ESMO 2025; Hecht JR, Lancet 2025.

STELLAR-316: Phase 3 Trial of Zanzalintinib +/- Atezolizumab in Pts with Resected Stage II/III CRC

ALAMEDA, Calif. & AUSTIN, Texas, January 07, 2026--(BUSINESS WIRE)--Exelixis, Inc. (Nasdaq: EXEL) and Natera (Nasdaq: NTRA), a global leader in cell-free DNA and precision medicine, today announced their collaboration on the planned Exelixis-sponsored STELLAR-316 trial. This randomized phase 3 pivotal trial will evaluate zanzalintinib, Exelixis' novel oral kinase inhibitor, with and without an immune checkpoint inhibitor, in patients with resected stage II/III colorectal cancer (CRC).

Using Natera's Signatera™ test following completion of definitive therapy*, patients with CRC who test positive for molecular residual disease (MRD) and have no radiographic evidence of disease will be eligible for enrollment in the STELLAR-316 trial. Working with patients and their providers, this trial will be fully enrolled with patients who are receiving commercial Signatera testing as part of their routine standard of care.

The primary endpoint of STELLAR-316 is disease-free survival. Signatera will also be used for longitudinal monitoring of circulating tumor DNA clearance, one of the secondary endpoints of the trial. Exelixis expects to initiate STELLAR-316 in mid-2026.

VANDERBILT UNIVERSITY MEDICAL CENTER

*Definitive therapy: colon = adjuvant chemotherapy; rectal = total neoadjuvant therapy

QUESTIONS?

Module 11: Colorectal Cancer (CRC)

Current and Future Role of Immune Checkpoint Inhibition in the Management of CRC — Dr Ciombor

Other Recent Advances in CRC Management — Dr Strickler

Other Recent Advances in CRC

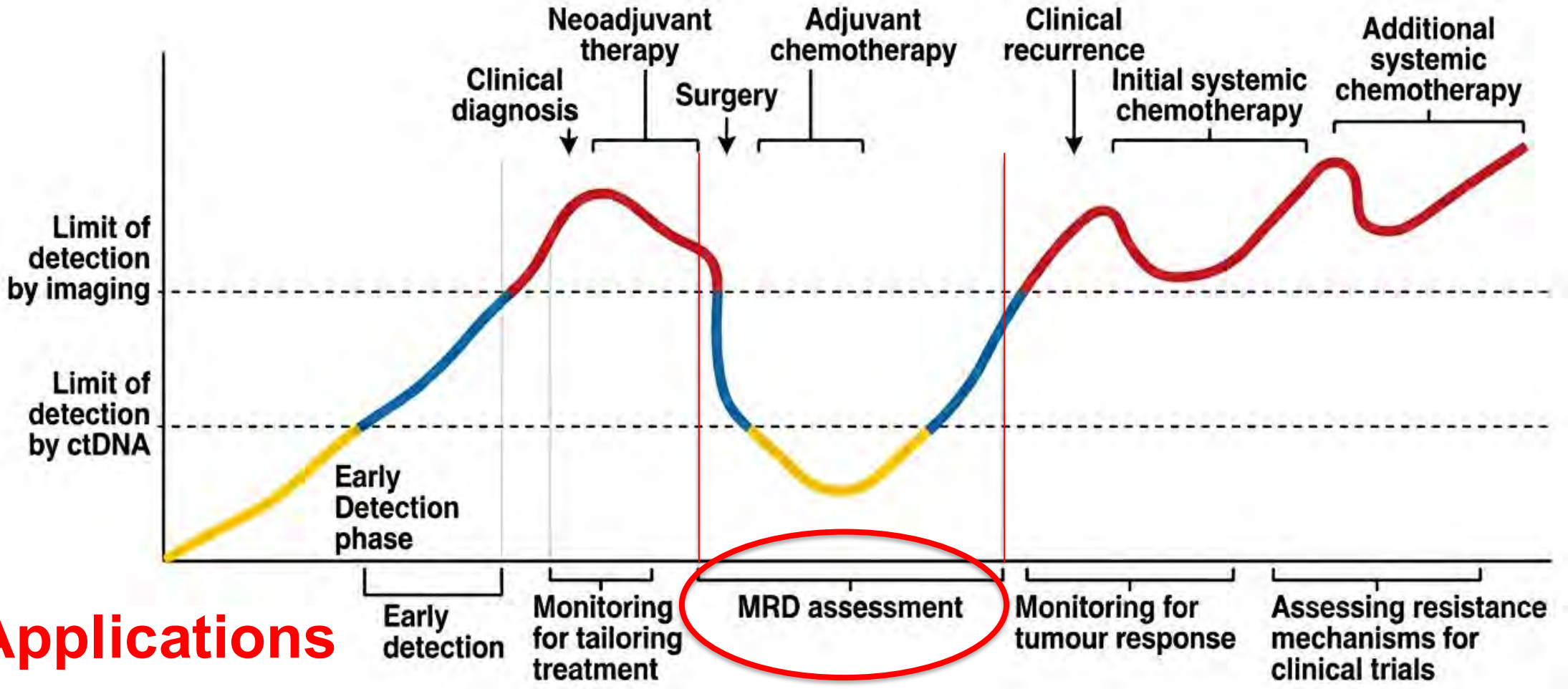
John Strickler, MD
Professor of Medicine
Duke University
April 26, 2026

Disclosures

Advisory Committees	AbbVie Inc, Alterome Therapeutics, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeOne, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Cytovation ASA, Daiichi Sankyo Inc, Exelixis Inc, Full-Life Technologies, GE Healthcare, Genentech, a member of the Roche Group, GSK, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, Leap Therapeutics Inc, Lilly, Merck, Natera Inc, Pfizer Inc, Pheon Therapeutics, Quanta Therapeutics Inc, Regeneron Pharmaceuticals Inc, Revolution Medicines Inc, Sanofi, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tempus, Xilio Therapeutics
Contracted Research	AbbVie Inc, Alterome Therapeutics, Amgen Inc, Apollo Therapeutics, Astellas, Bayer HealthCare Pharmaceuticals, BeOne, Daiichi Sankyo Inc, Erasca, Genentech, a member of the Roche Group, GSK, Leap Therapeutics Inc, Lilly, Novartis, Pfizer Inc, Quanta Therapeutics Inc, Regeneron Pharmaceuticals Inc, Revolution Medicines Inc
Data and Safety Monitoring Boards/Committees	AbbVie Inc, Johnson & Johnson
Stock OPTIONS — Private Companies	Triumvira Immunologics

What is the mechanistic rationale for ctDNA-based MRD monitoring in the management of CRC?

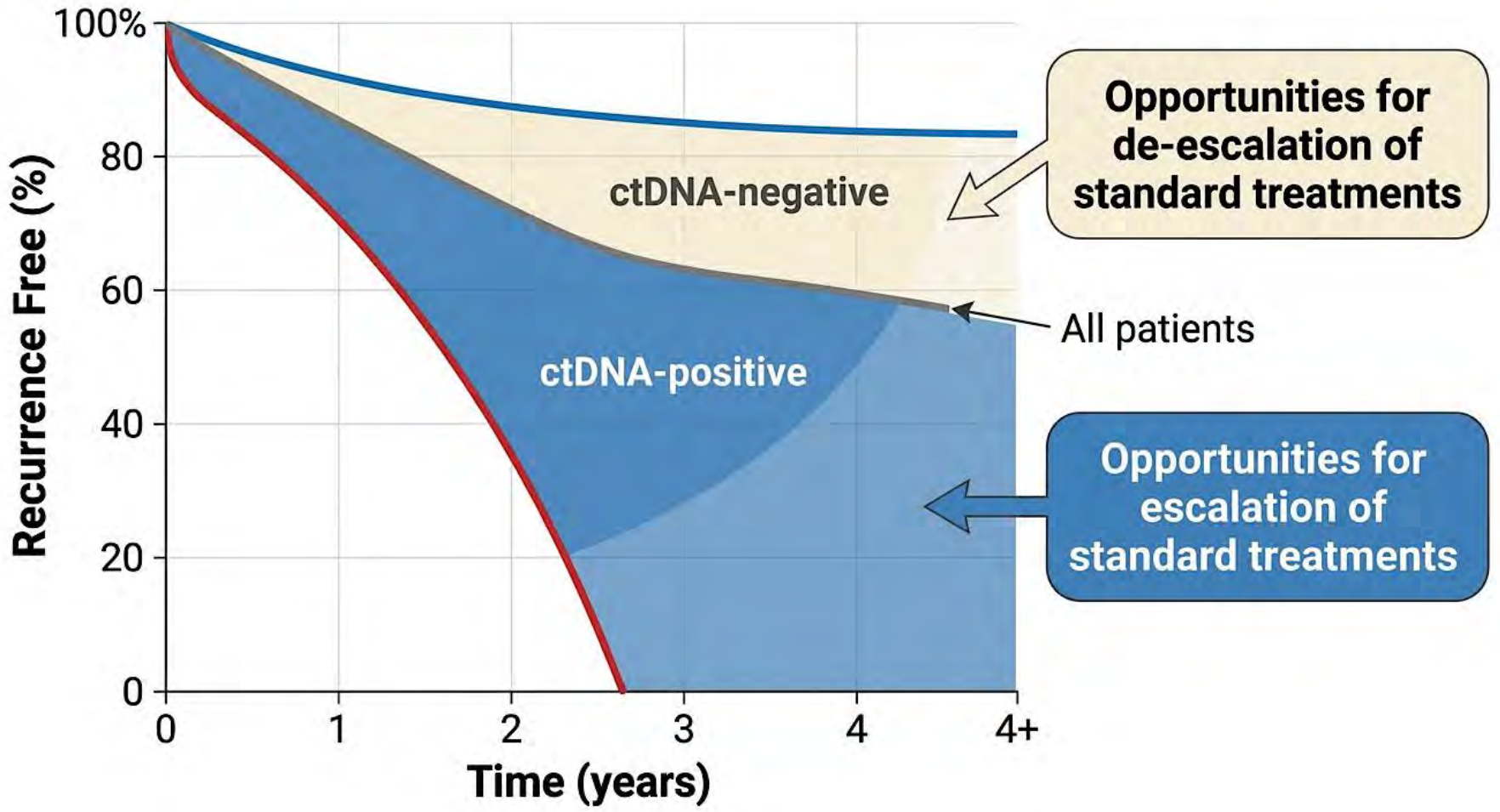
Clinical applications for ctDNA



Applications

Dasari et al., *Nat Rev Clin Oncol*. 2020 Dec; 17(12) 757-770.

Goal of MRD testing: Incorporate recurrence risk into clinical decision-making



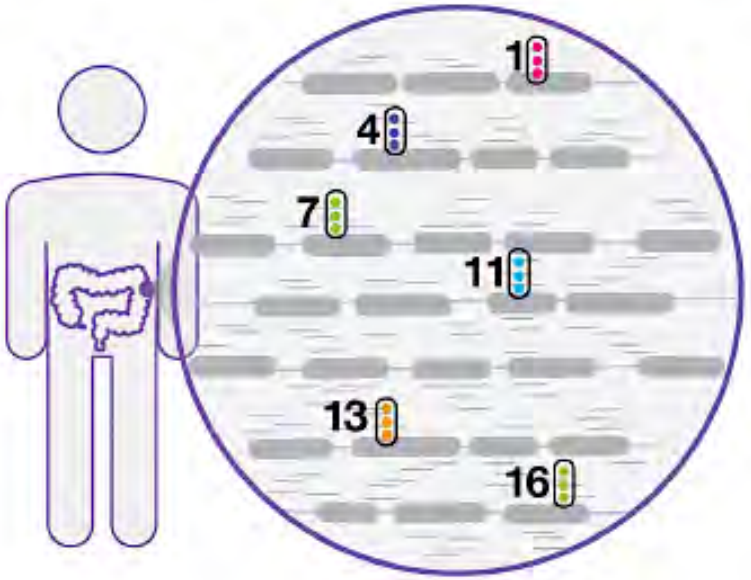
Dasari et al., *Nat Rev Clin Oncol*. 2020 Dec; 17(12) 757-770.

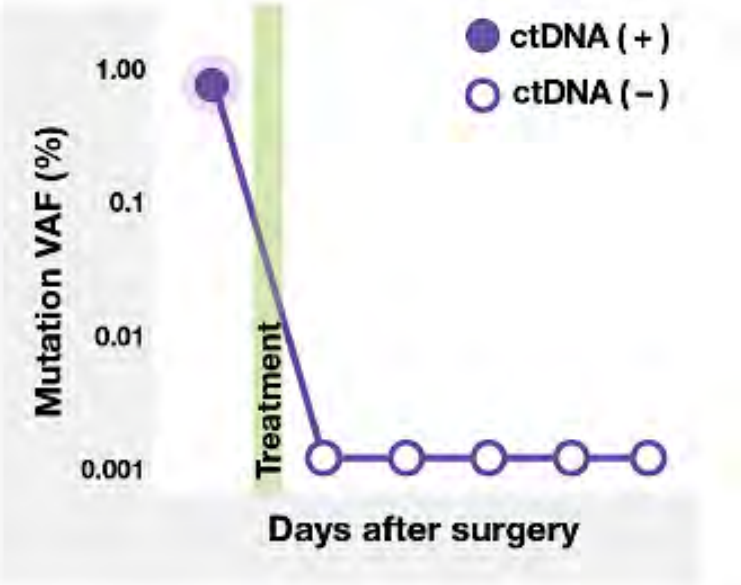
Option 1: “Tumor informed” MRD

Sequencing of tumor tissue, to identify unique signature of tumor mutations

Custom design and manufacture of personalized mPCR assay for each patient, targeting the top 16 clonal mutations found in tumor

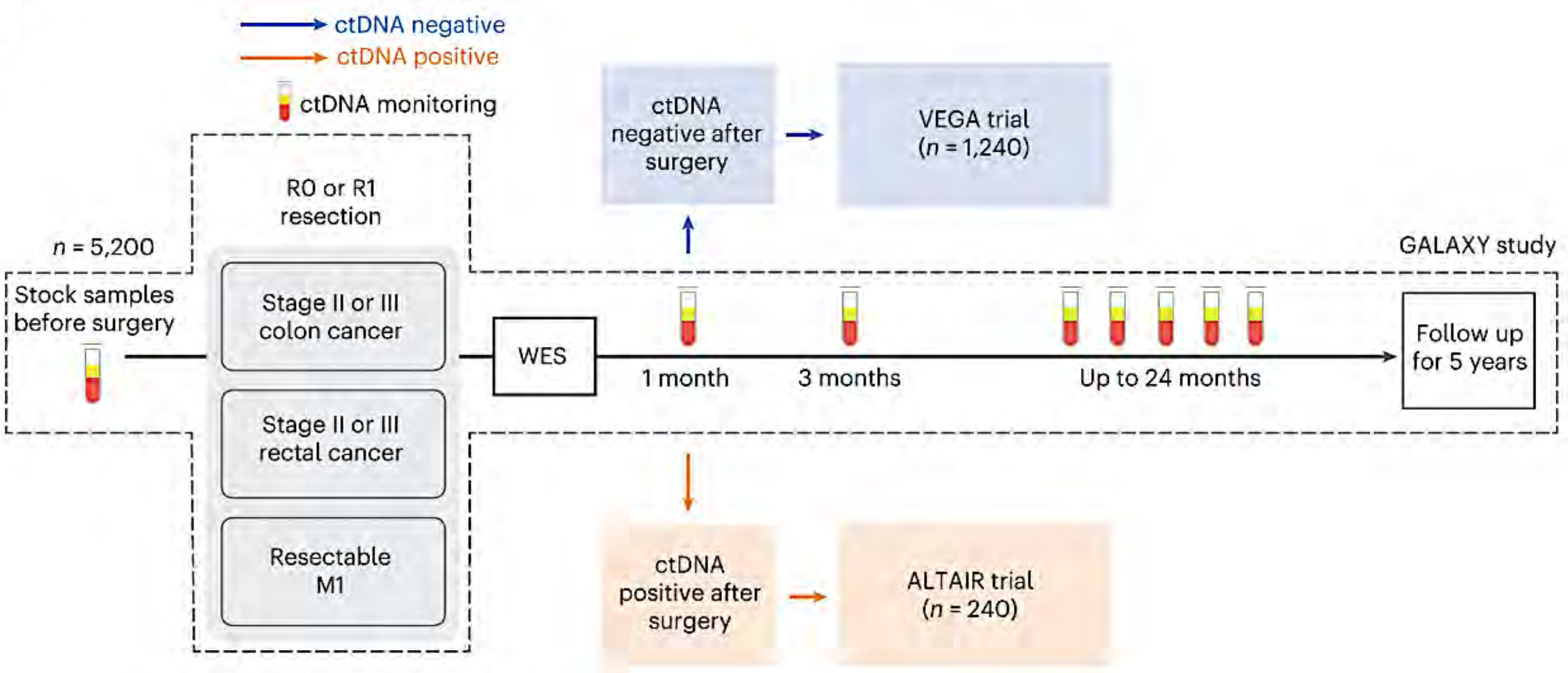
Use personalized assay to test patient’s blood for presence of circulating tumor DNA (ctDNA)





Lieu et. al., J Clin Oncol 42, 2023 (3_suppl; TPS243). Presented at ASCO GI 2024

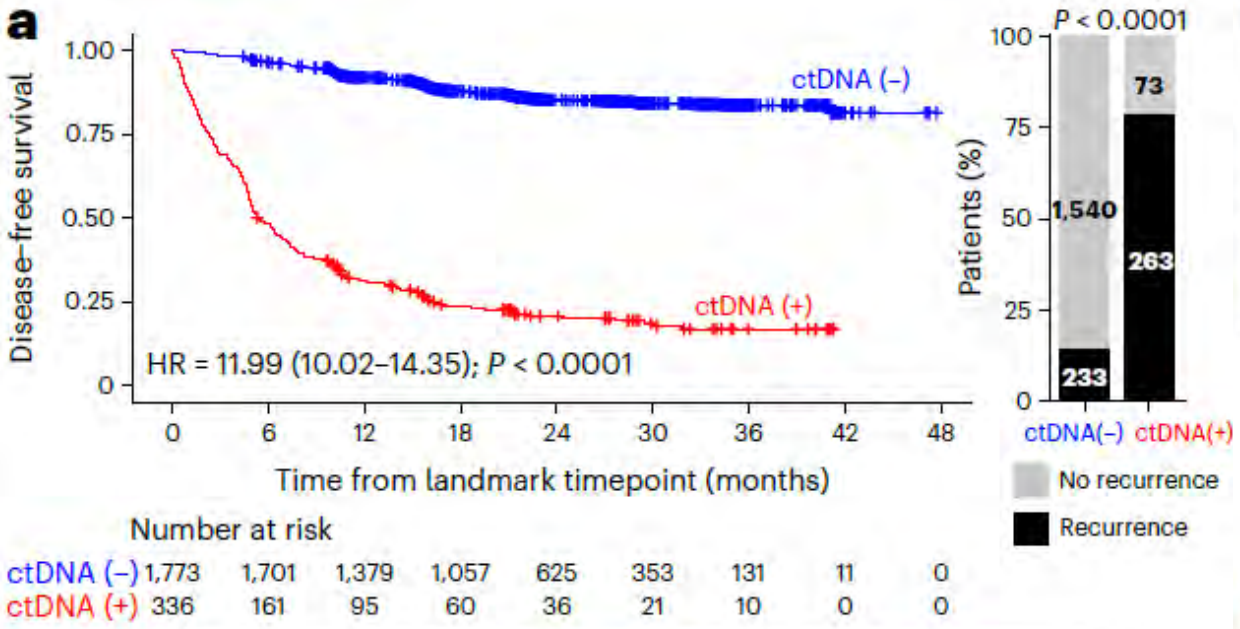
Clinical validation of tumor informed MRD testing: GALAXY Study Design



Kotani et. al., Nature Medicine (2023) 29, 127–134.
Nakamura et. al., Nature Medicine (2024) 30, 3272–3283.

MRD status after surgery is strongly prognostic

Disease-free survival

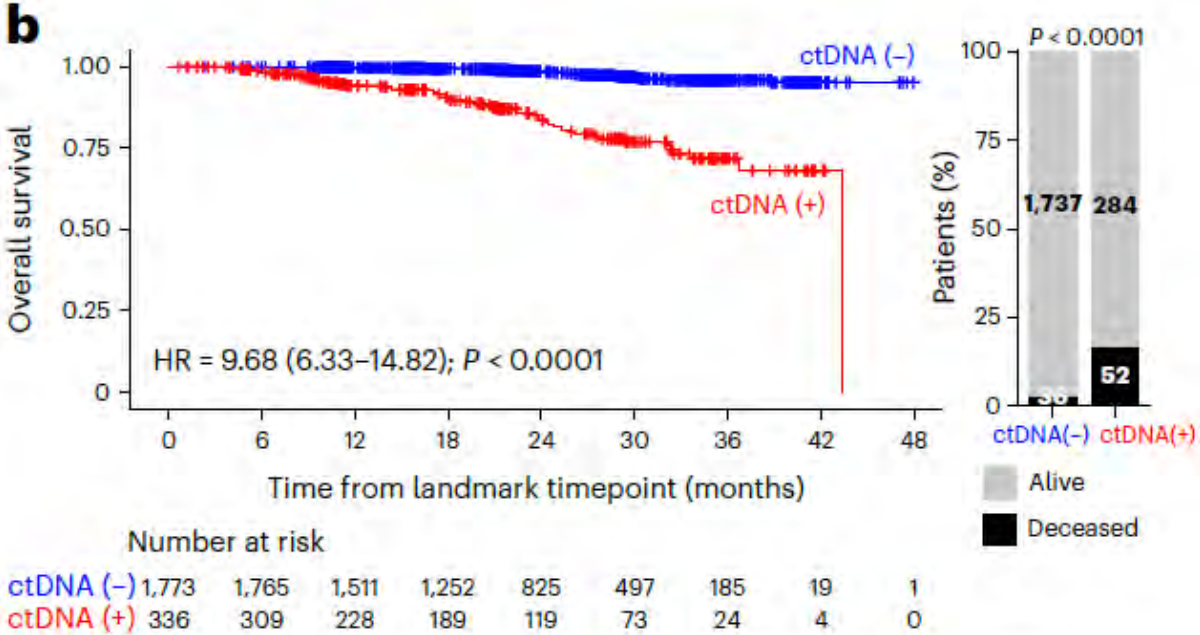


Number at risk

ctDNA (–)	1,773	1,701	1,379	1,057	625	353	131	11	0
ctDNA (+)	336	161	95	60	36	21	10	0	0

ctDNA status	Negative	Positive
Events %	13.14 (233/1773)	78.27 (263/336)
24M-DFS % (95% CI)	85.10 (83.20–86.9)	20.57 (16.14–25.37)
30M-DFS % (95% CI)	84.10 (82.0–86.0)	18.50 (14.0–23.40)
36M-DFS % (95% CI)	83.50 (81.20–85.60)	16.70 (12.10–21.90)
mDFS (mo)	NR	5.34 (4.83–6.70)

Overall survival



Number at risk

ctDNA (–)	1,773	1,765	1,511	1,252	825	497	185	19	1
ctDNA (+)	336	309	228	189	119	73	24	4	0

ctDNA status	Negative	Positive
Events %	2.03 (36/1773)	15.48 (52/336)
24M-OS % (95% CI)	98.50 (97.70–99.10)	83.65 (77.84–88.06)
30M-OS % (95% CI)	96.80 (95.40–97.80)	76.90 (69.80–82.50)
36M-OS % (95% CI)	96.0 (94.30–97.20)	71.80 (63.40–78.60)
mOS (mo)	NR	43.40 (NR–NR)

ctDNA positivity preceded radiological recurrence by a median of 5.9 months (range, 0–33.1)

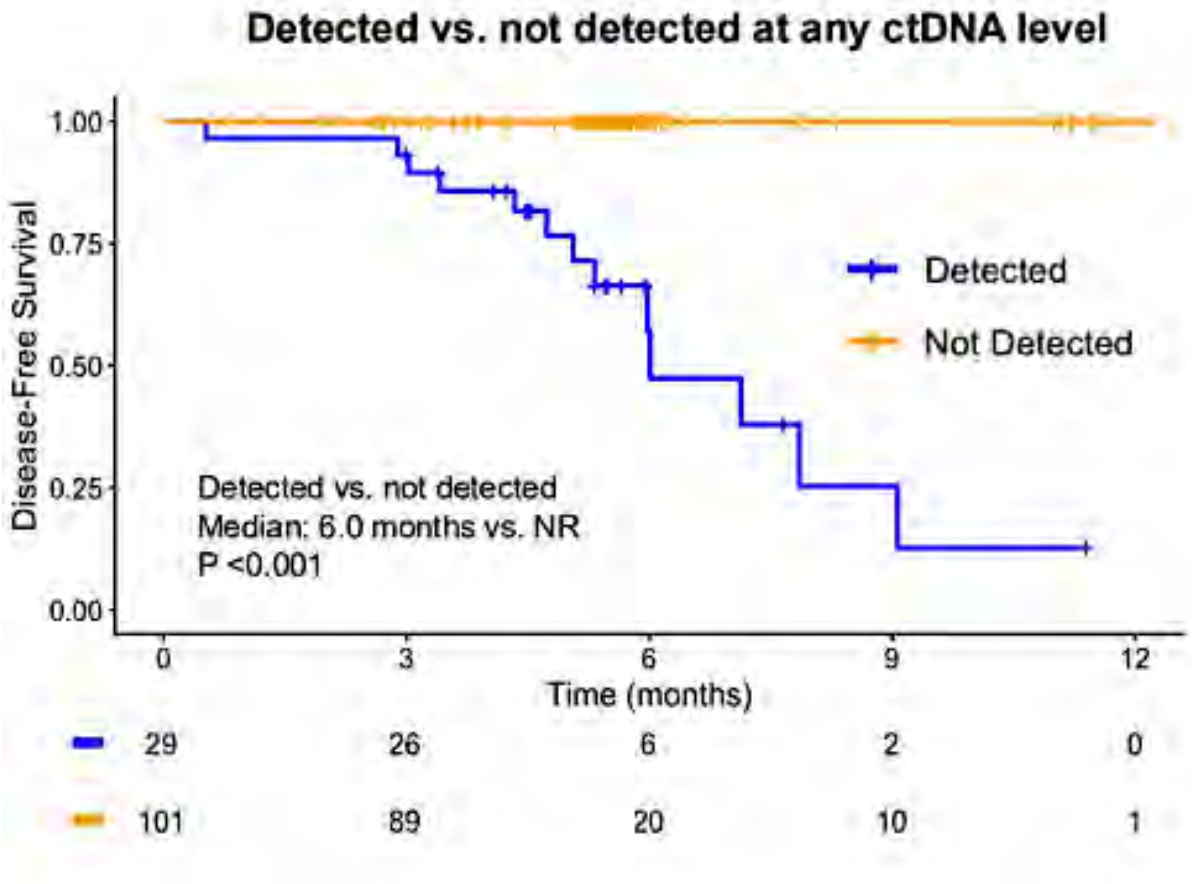
Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

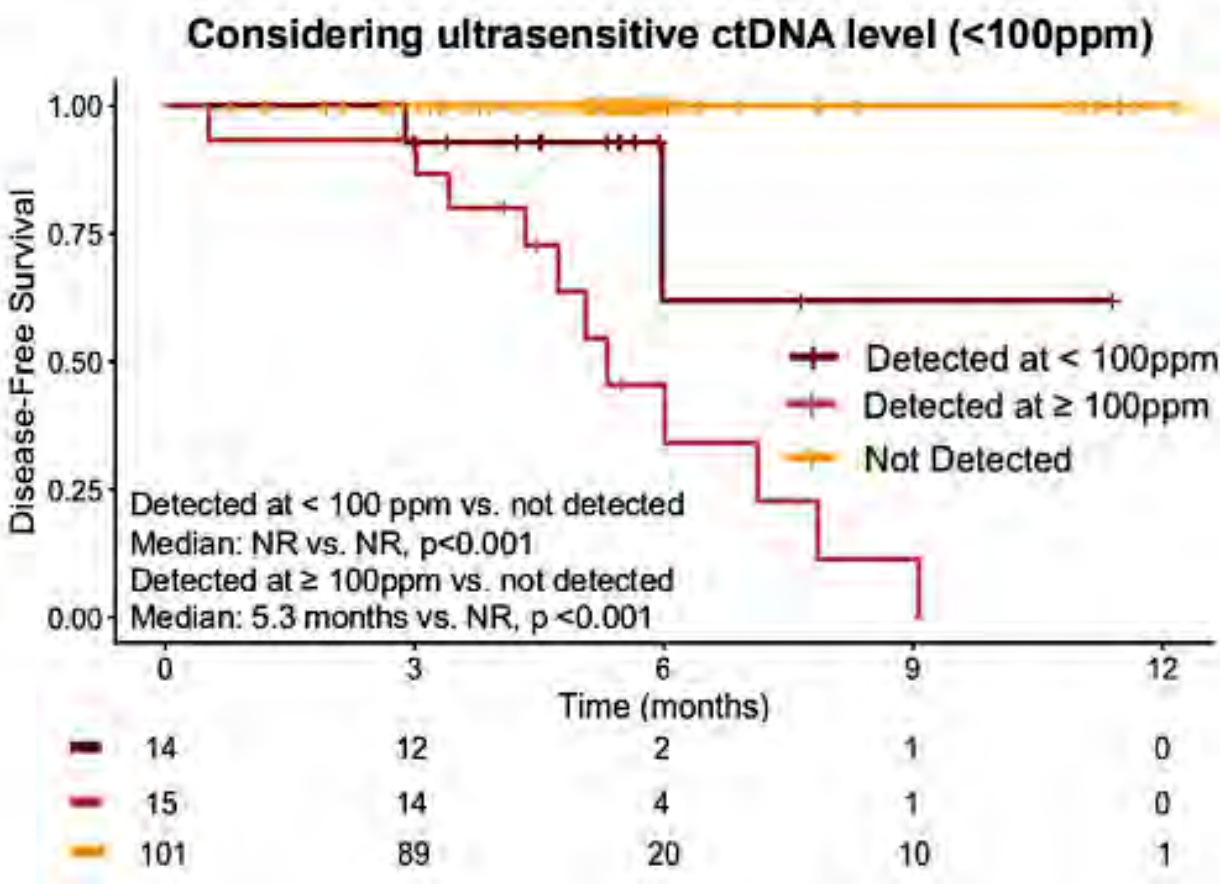
Whole genome (WGS) MRD: More sensitive?

Disease-free survival – Myriad (WGS) MRD assay

184 patients enrolled, 154 patients with post-1M ctDNA asessment, 109 patients with post-6M ctDNA assessment

Single post-operative timepoint 1 month from surgery (Stage I-IV CRC, s/p resection), N=130



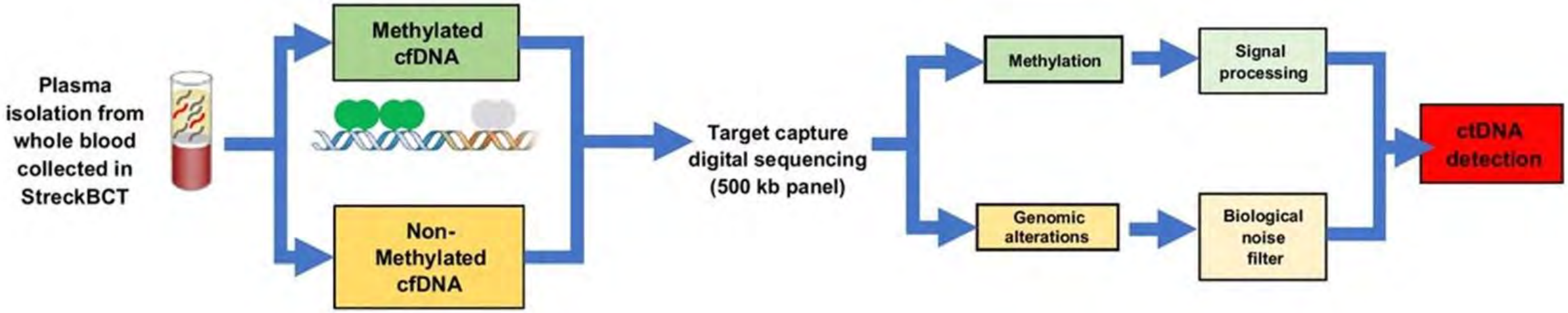


13/13 recurrences detected at any ctDNA level; Specificity 86% (101/117) at any ctDNA level

Kagawa et. al., Presented at ASCO GI 2026. J Clin Oncol 44, 2026 (suppl 2; abstr 187)

Option 2: “Tumor naïve” MRD

Example: Guardant Lunar Assay (Version 1.0)

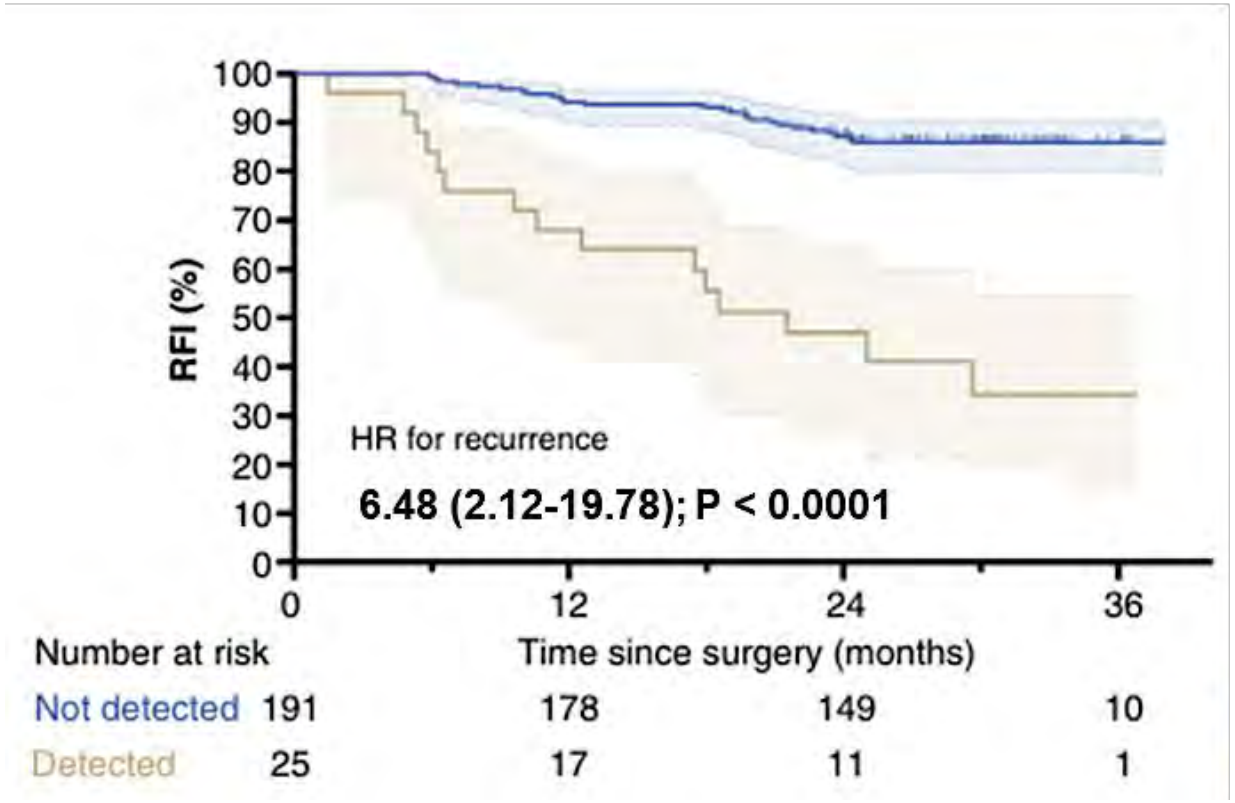


Parikh et al., Clin Cancer Res. 2021; Presented at ASCO GI 2024

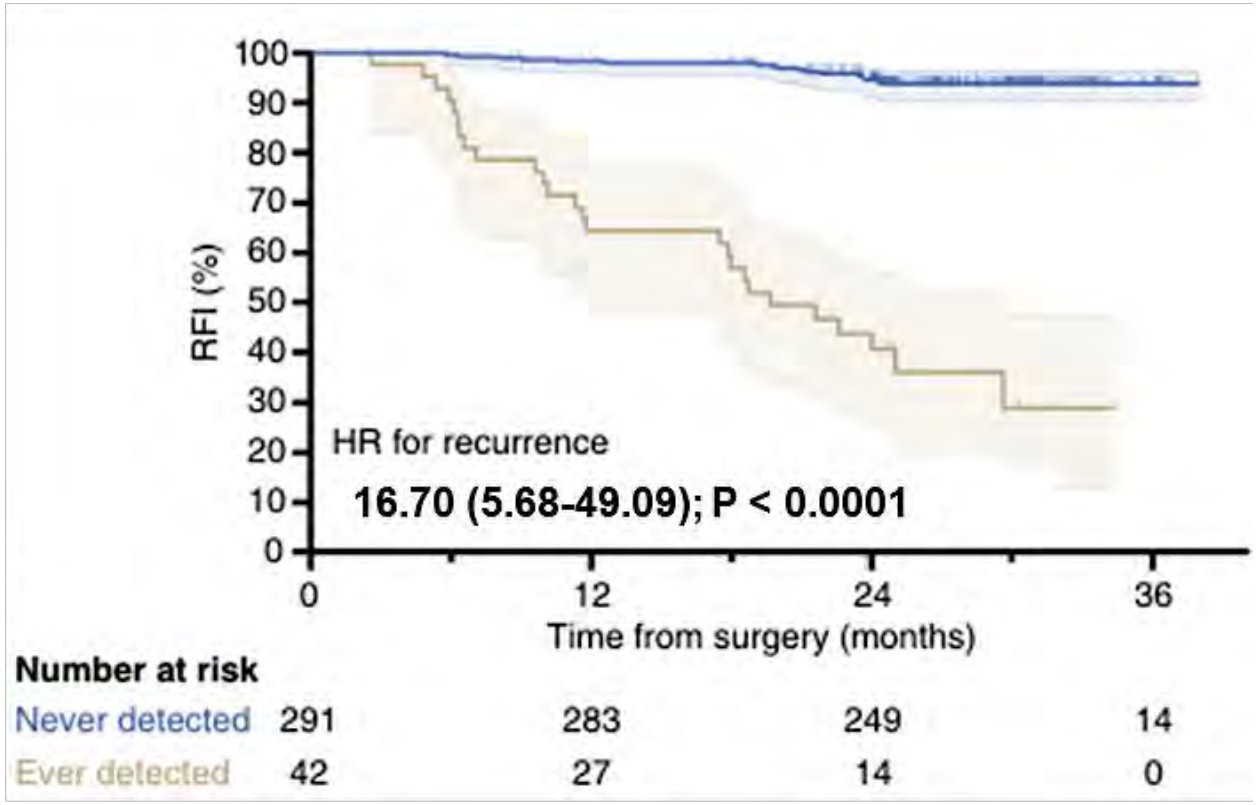
“Tumor naive” MRD: COSMOS-CRC-01 Trial

Study evaluating perioperative MRD using Guardant REVEAL for colorectal cancer

Single post-operative timepoint (+28 days)



Serial surveillance



Nakamura Y, Tsukada Y, Matsuhashi N, et al. Clin Cancer Res 2024

ctDNA (MRD) detection assays in the clinic

Tumor-informed assays

Assay	Development Company / Academia	Tumor Tissue Analysis	Number of target gene mutations
Signatera	Natera	Whole exome	16
RaDaR	NeoGenomics	Whole exome	48
Invitae PCM	Invitae	Whole exome	50
Oncodetect	Exact Sciences	Whole exome	up to 200
Signatera	Natera	Whole genome	64
NEXT Personal	Personalis	Whole genome	up to 1,800
MAESTRO	Broad Institute	Whole genome	1000
Precise MRD	Myriad Genetics	Whole genome	Up to 1000

Tumor-naïve assays

Assay	Development Company / Academia	Analysis population
Guardant Reveal	Guardant Health	DNA methylation
xM	Tempus	DNA methylation/genetic alteration
-	GRAIL	DNA methylation
Latitude	Natera	DNA methylation

Slide credit: Takayuki Yoshino (slide modified/ updated)

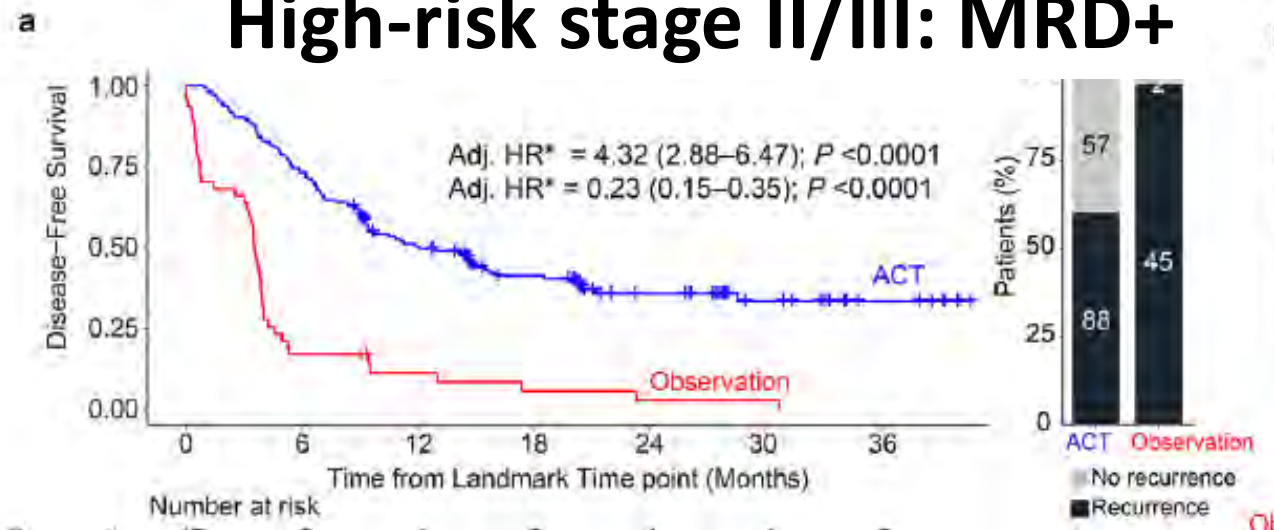
What is the mechanistic rationale for ctDNA-based MRD monitoring in the management of CRC?

- Objective of MRD testing: Detect disease before radiographic evidence of macroscopic disease
- 2 categories of MRD tests:
  - Tumor informed: “Whole Exome” or “Whole Genome”
  - Increased number of target gene mutations increases sensitivity, but incremental clinical value is not well defined
  - Tumor-naive tests also have advantages (speed & convenience)
- There are no head-to-head comparisons between assays

What evidence exists for ctDNA-based MRD monitoring in early stage and advanced CRC?

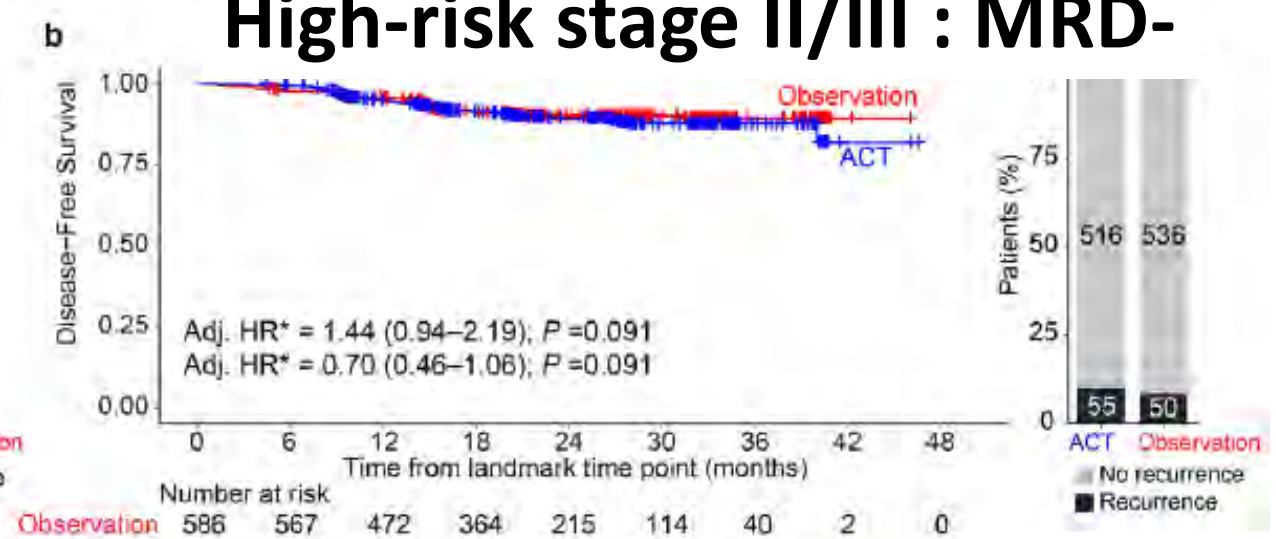
GALAXY: Adjuvant chemotherapy for high-risk stage II/III disease

High-risk stage II/III: MRD+



Treatment	ACT	Observation
Events %	60.68 (88/145)	95.74 (45/47)
24M-DFS % (95% CI)	35.83 (27.41–44.32)	2.84 (0.23–12.35)
mDFS (mo)	12.06 (9.30–18.57)	3.55 (3.16–3.95)

High-risk stage II/III : MRD-



Treatment	ACT	Observation
Events %	9.63 (55/571)	8.53 (50/586)
24M-DFS % (95% CI)	89.11 (85.81–91.68)	89.9 (86.80–92.30)
mDFS (mo)	NR	NR

Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

DYNAMIC Study Design

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo**
  (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

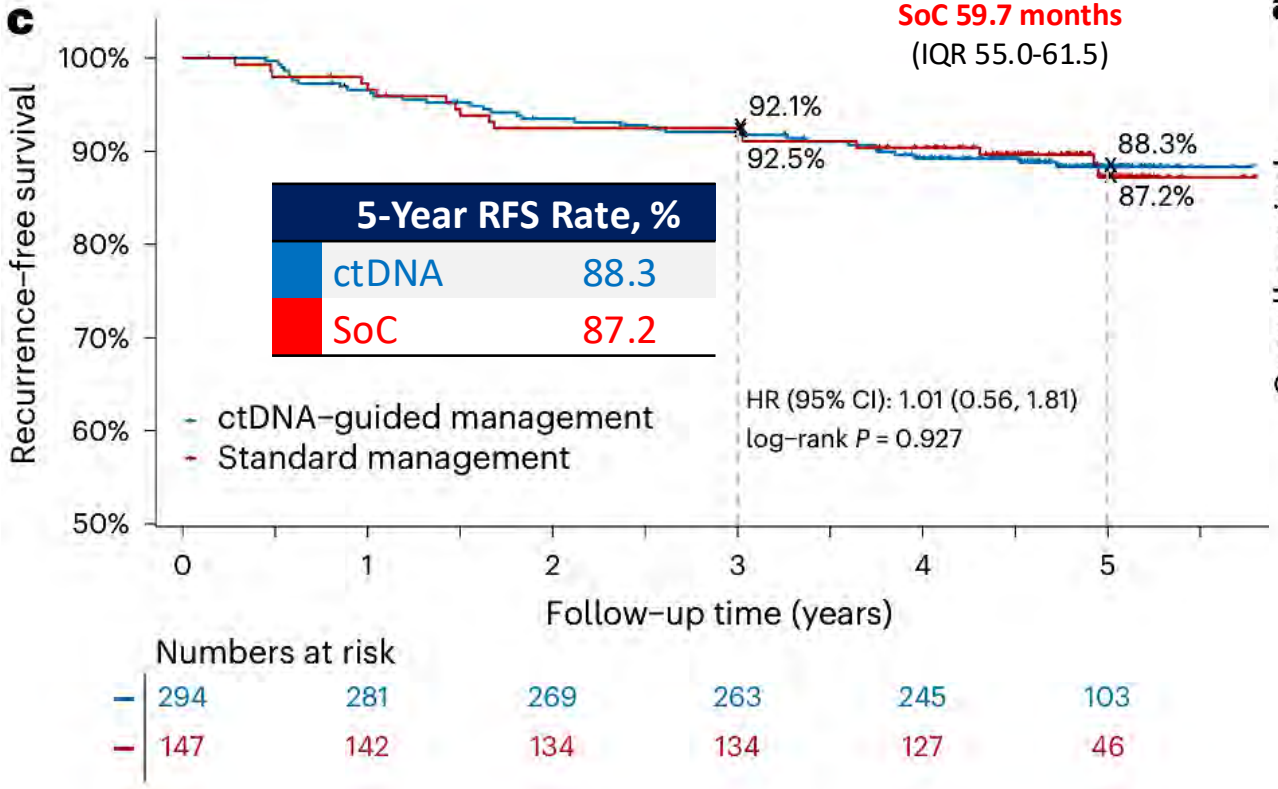
Tie et al., N Engl J Med 2022;386:2261-72.Presented at 2022 ASCO Annual Meeting

DYNAMIC: Updated 5-year RFS and Overall survival

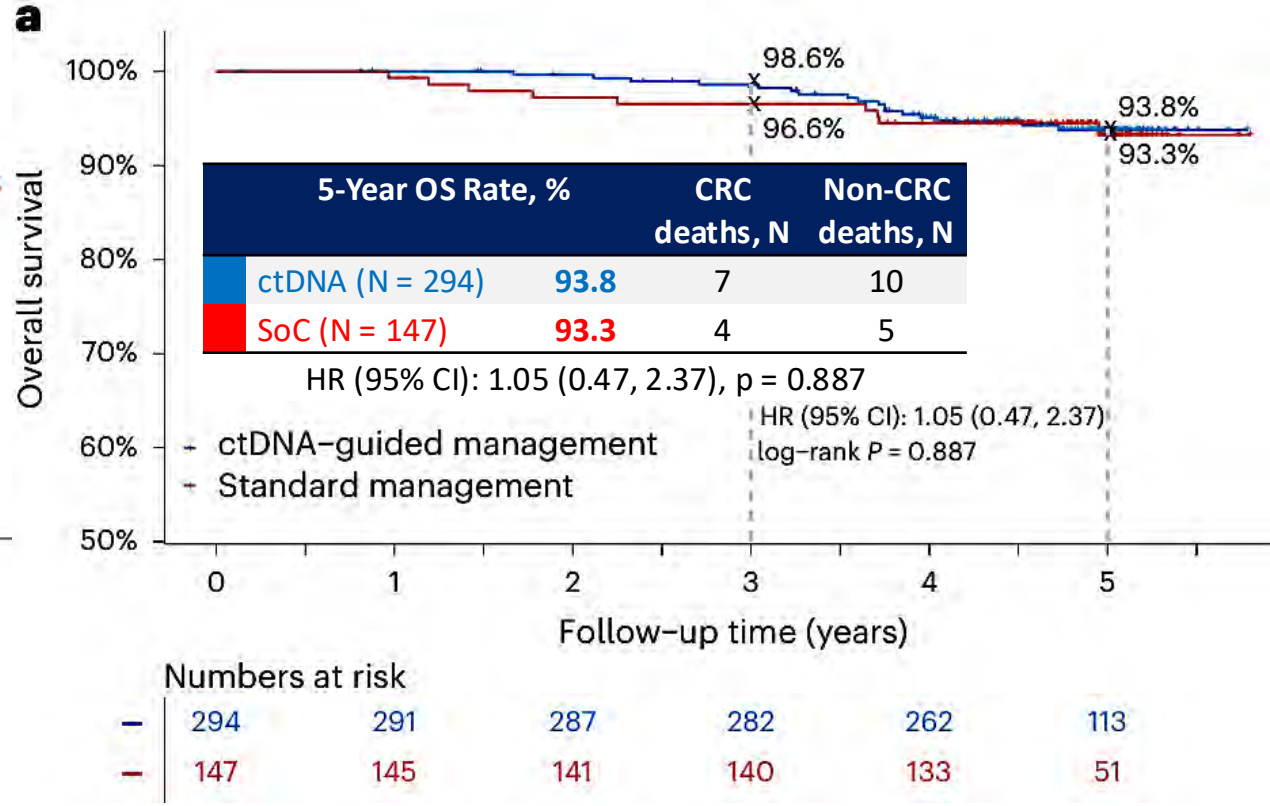
Updated 5-Year RFS Analysis

Difference in 5-year RFS rate +1.1%
(95% CI for difference, -5.8 to 8.0%)

Median Follow-Up
ctDNA-Guided 59.7 months
SoC 59.7 months
(IQR 55.0-61.5)



Overall Survival



- **ctDNA-guided MRD-based adjuvant therapy significantly reduced the proportion of patients receiving postoperative adjuvant therapy compared to SOC based on conventional clinicopathological factors, while demonstrating non-inferiority in 5-year RFS/OS.**

Tie J, et al. Nature Medicine 2025

DYNAMIC-III Study Design

Randomized phase II/III trial: ctDNA-informed escalation versus standard management

Stage III Colon Cancer

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

Tumor-Informed ctDNA Analysis
(SaferSeqS[1] targeted CRC panel)

W5-6

R 1:1

Clinicians nominate SoC Chemo

ctDNA-Informed Management

- ctDNA-Negative → De-escalate
- ctDNA-Positive → Escalate

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Pre-Planned SoC → Escalation
No chemotherapy → 5FU/Cape
5FU/Cape → 6M Oxaliplatin doublet
3M Oxaliplatin doublet → 6M Doublet or ≥ 3M FOLFOXIRI
6M Oxaliplatin doublet → ≥ 3M FOLFOXIRI

Standard Management

Treatment per clinician's choice (blinded to ctDNA result)

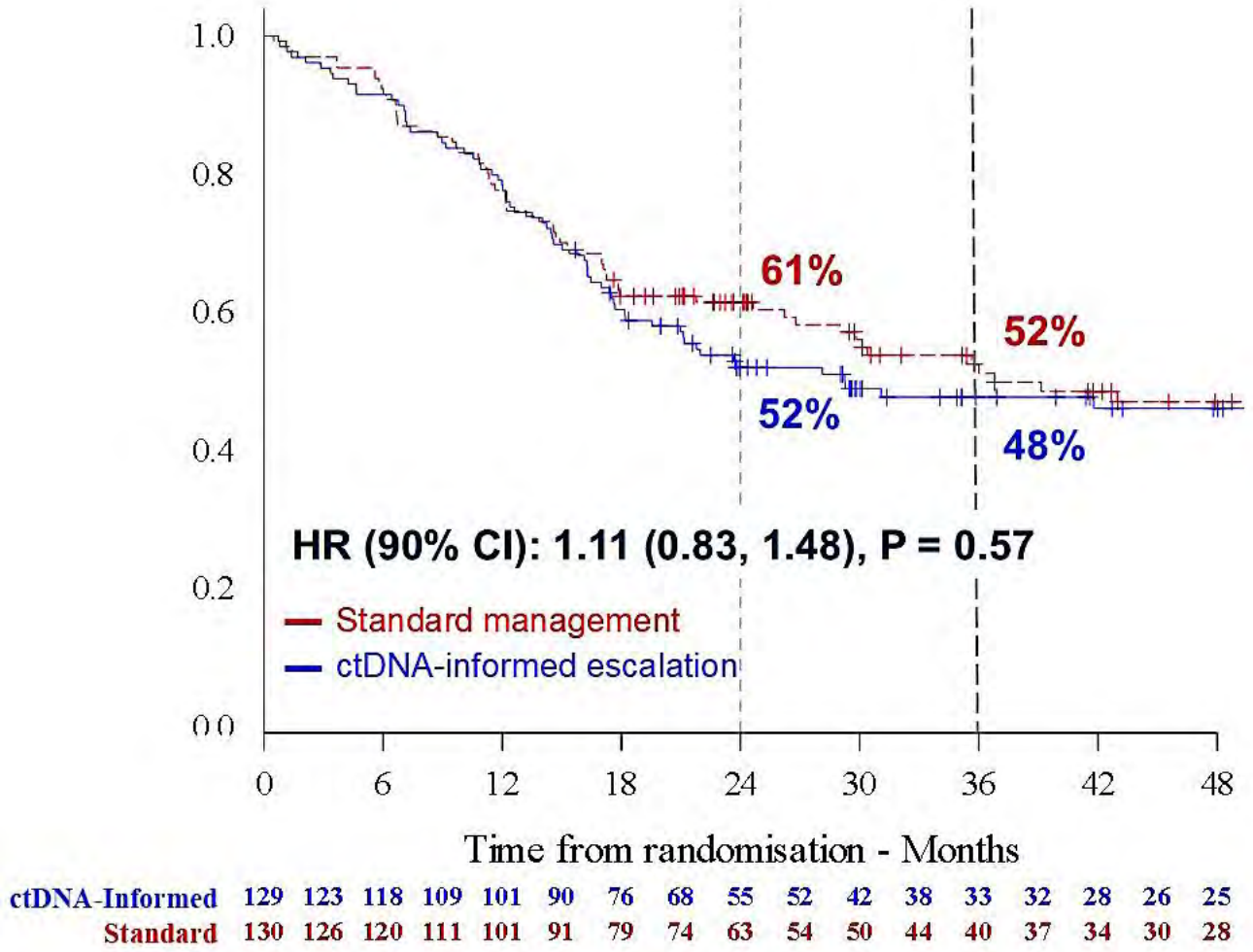
Stratified by clinical risk (low vs high) and sites

Primary Analysis of ctDNA-Positive Cohort: Endpoints to be Presented	
Primary: 2 years RFS	**Secondary:** safety, end-of-treatment (EoT) ctDNA clearance
	Exploratory: post-operative ctDNA levels

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Tie et al., J Clin Oncol. 2025;43:16_suppl. 3503; Presented at 2025 ASCO Annual Meeting

DYNAMIC-III: Recurrence-Free Survival for ctDNA+

Randomized phase II/III trial: ctDNA-informed escalation versus standard management



	Total	Events	Median RFS (mths)	2-year RFS (90% CI)	3-year RFS (90% CI)
ctDNA	129	66	29.24	52% (44, 59)	48% (40, 55)
SoC	130	62	36.80	61% (54, 68)	52% (44, 60)

Median follow-up 42.2 months (0.78 - 63.0)

Data cut-off: 14 Nov 2024

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Tie et al., J Clin Oncol. 2025;43:16_suppl. 3503; Presented at 2025 ASCO Annual Meeting

DYNAMIC-III Study Design

Randomized phase II/III trial: ctDNA-informed de-escalation versus standard management

Stage III Colon Cancer

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

Tumour-Informed ctDNA Analysis
(SaferSeqS[1] targeted CRC panel)

W5-6

R 1:1

Clinicians nominate SoC Chemo

ctDNA-Informed Management

- ctDNA-Negative ➔ De-escalate
- ctDNA-Positive ➔ Escalate

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Pre-Planned SoC ➔ De-escalation

6M FP ➔ No chemo or 3M FP
3M Oxaliplatin + FP ➔ 3-6M FP
6M Oxaliplatin + FP ➔ 3M Oxaliplatin + FP or 6M FP

FP = fluoropyrimidine

Standard Management

Treatment per clinician's choice (blinded to ctDNA result)

Stratified by clinical risk (low vs high) and sites

Primary Analysis of ctDNA-Negative Cohort: Endpoints to be Presented Here

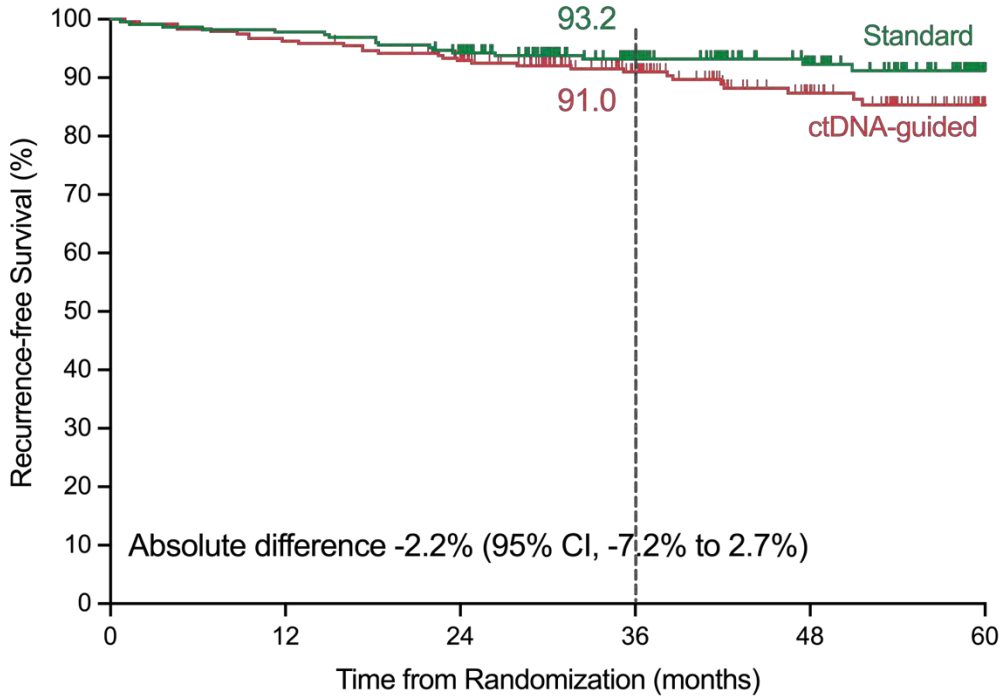
Primary: 3-year recurrence-free survival (RFS)	Secondary: treatment adherence, safety

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Tie et al., J Clin Oncol. 2025;43:16_suppl. 3503; Presented at 2025 ASCO Annual Meeting

DYNAMIC-III: RFS for ctDNA negative

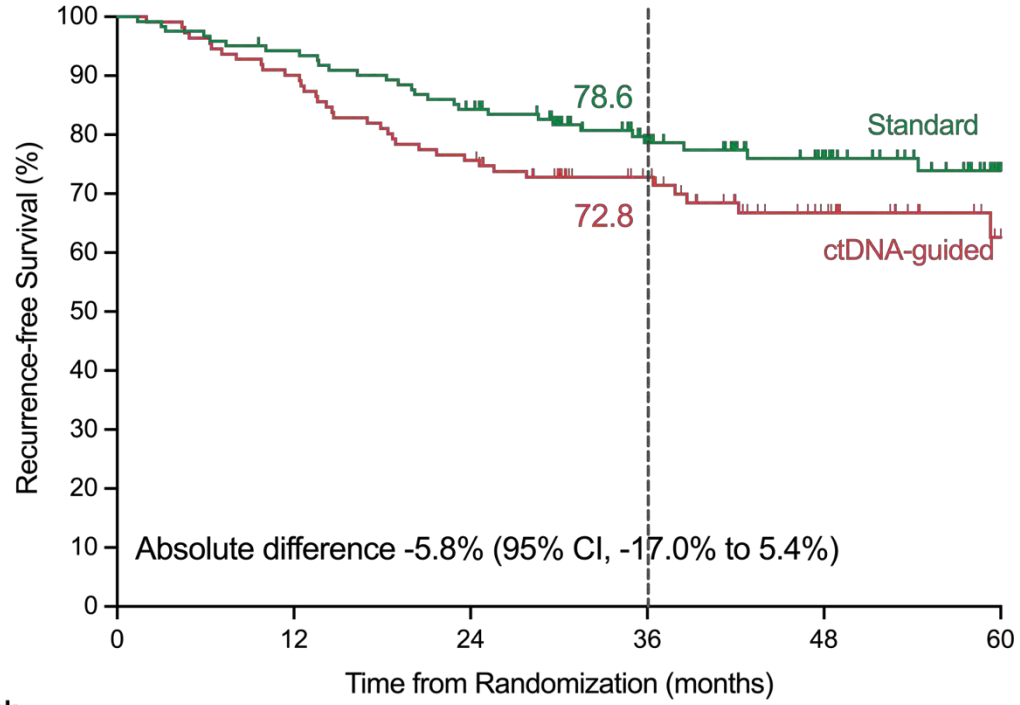
Randomized phase II/III trial: ctDNA-informed de-escalation versus standard management

Clinical Low Risk (T1-3N1)



No. at Risk						
ctDNA-guided	242	233	219	160	93	39
Standard	227	222	209	152	95	32

Clinical High Risk (T4 and/or N2)



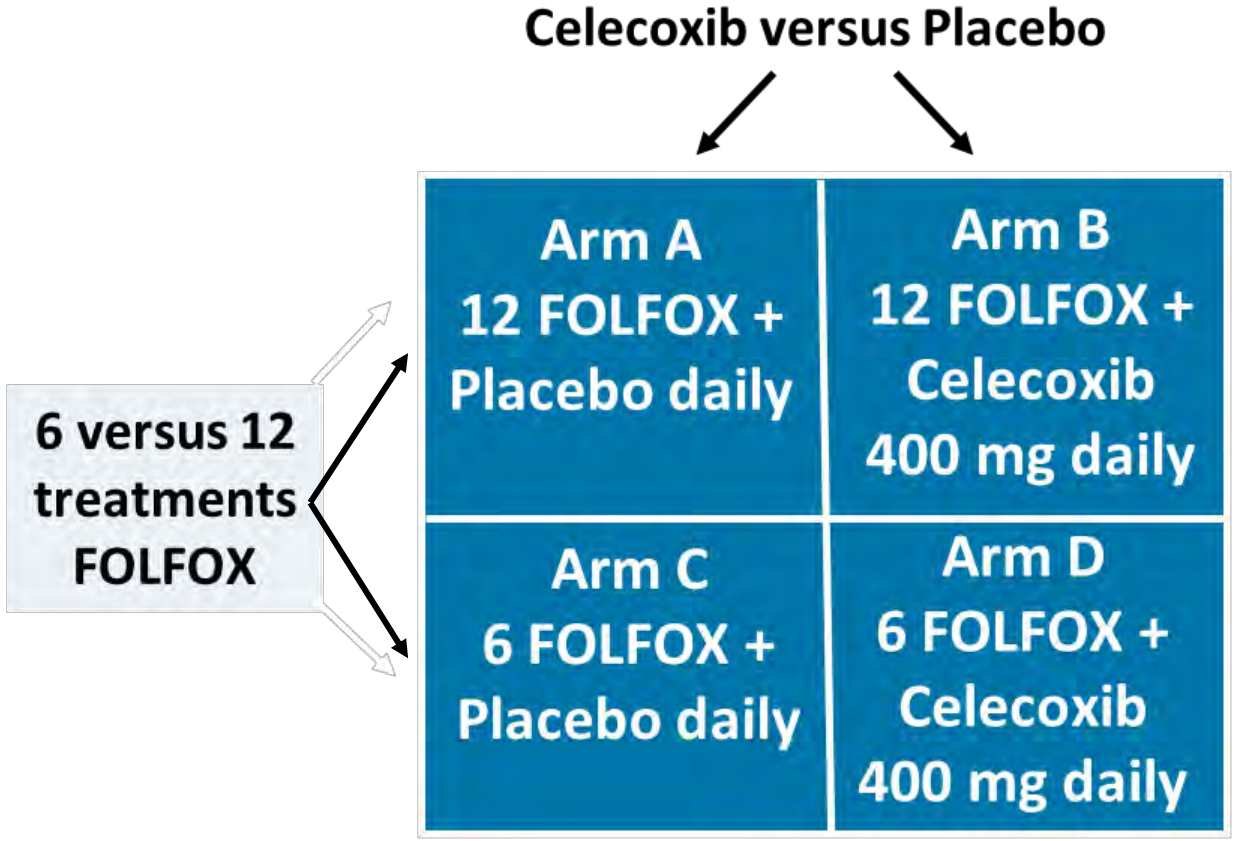
No. at Risk						
ctDNA-guided	111	100	84	54	31	12
Standard	122	114	101	71	48	14

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Presented at 2025 ESMO Congress

CALGB/SWOG 80702 trial design

Key eligibility criteria

- Resected adenocarcinoma of the colon without metastatic disease
- At least one pathologically confirmed positive lymph node or N1c disease as defined in AJCC version 7
- Patients ineligible if they use NSAIDs at any dose more than 2x / week or aspirin at more than 325 mg 3x / week. Low-dose aspirin not exceeding 100 mg/day *permitted*

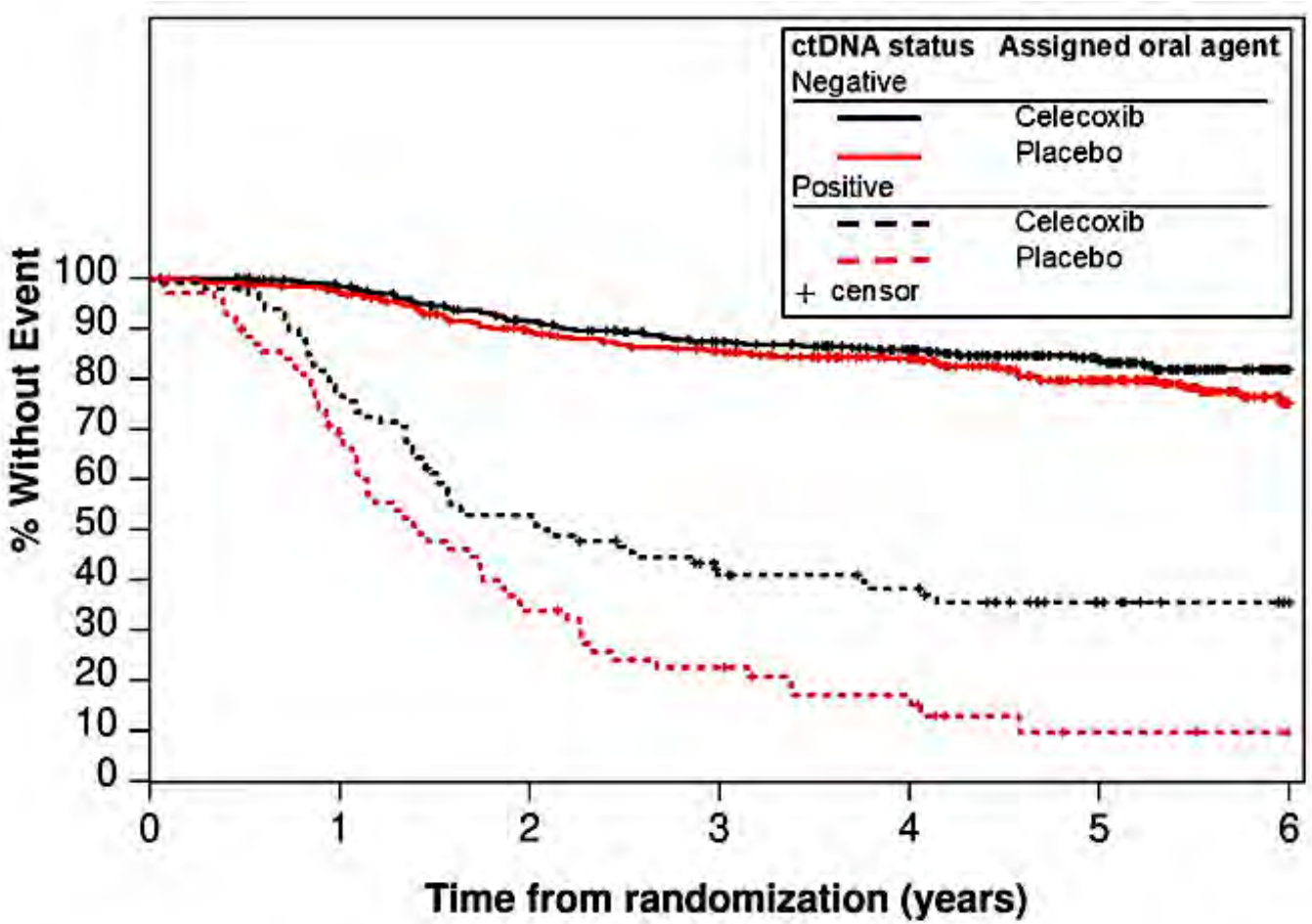


Celecoxib/placebo continued for a total of 3 years from the day study drug was initiated

Target sample size = 2,500
Actual final accrual = 2,526

Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

Celecoxib associated with DFS benefit in ctDNA+ colon cancer



Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.1293[4]
Celecoxib	58/375	0.76 (0.54-1.08)	87.4 (84.0-91.0%)	
Placebo	73/392	Reference	85.6 (82.0-89.4%)	
Positive				0.0013[4]
Celecoxib	61/99	0.55 (0.39-0.80)	41.0 (32.2-52.2%)	
Placebo	57/74	Reference	22.6 (14.3-35.5%)	
Interaction P-value: 0.1359[3]				

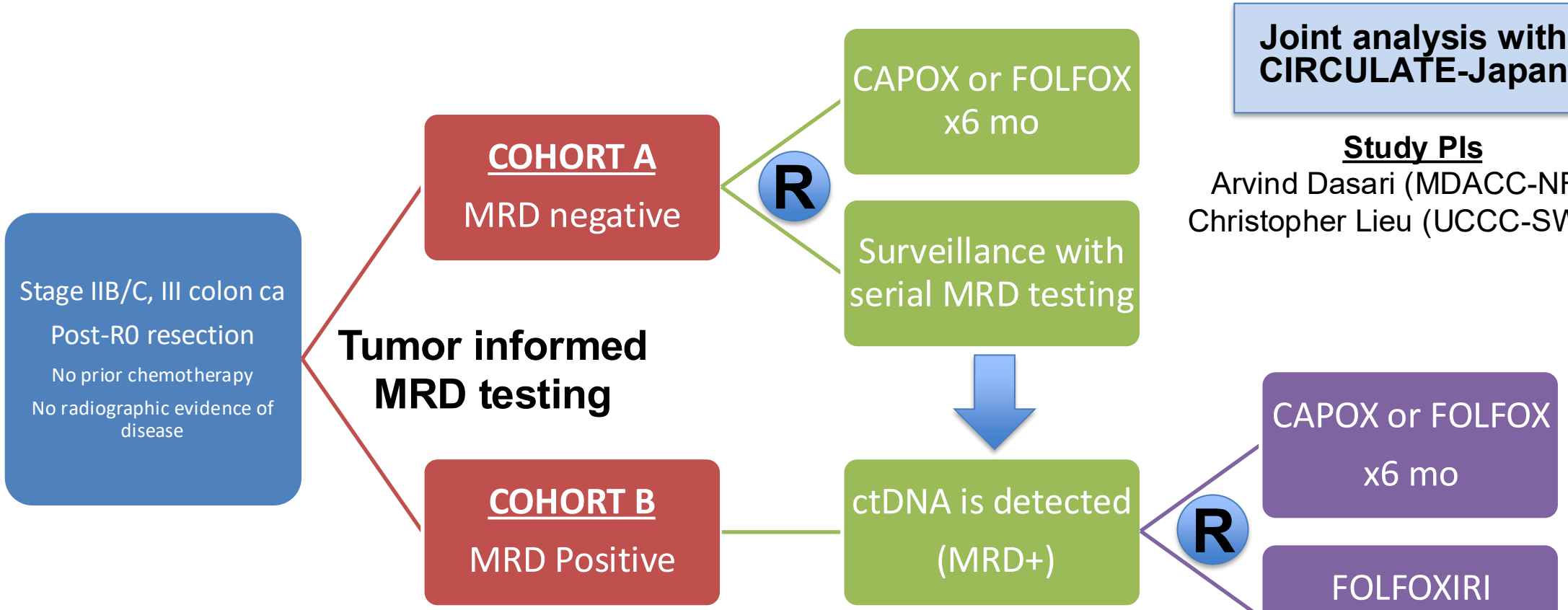
[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

What evidence exists for ctDNA-based MRD monitoring in early stage and advanced CRC?

- MRD status is strongly prognostic
- MRD testing has demonstrated clinical utility for patients with stage II (T3N0, MSS) colon cancer
- For patients with stage III colon cancer, there is not yet evidence we can de-escalate treatment based on a negative result, or escalate treatment based on a positive result
- Celecoxib (or aspirin?) can be considered for patients with MRD+ stage III colon cancer

CIRCULATE-US (NRG-GI008)



Primary endpoints

Cohort A: Ph2= Time to ctDNA conversion;
Ph 3 DFS (non-inferiority)
Cohort B: Ph2/3 DFS (superiority)

Lieu et. al., J Clin Oncol 42, 2023 (3_suppl; TPS243)

Clinical Trials for MRD+ CRC (US)

Immunotherapy trials

Source: https://crcmrd.com/

Name	Phase	Description	Enrollment
NCT06358430	I	TROP2-CAR-NK + cetuximab for MRD+ CRC.	Recruiting
ReLOAD NCT07071961	II	Regorafenib and lorigerlimab (PD-1 CTLA-4 DART) for MRD+ CRC	Not recruiting
NCT07136077	II	Fruquintinib and tislelizumab for MRD+ CRC	Recruiting
EMPIRE NCT07058012	II	Cemiplimab +/- fianlimab with other novel immunotherapy combinations for MRD+ disease	Not yet recruiting
COMBAT	II	Botensilimab and balstilimab regimen in CRC patients with MRD after definitive standard-of-care therapy	Not recruiting
NCT07227636	II	Botensilimab and balstilimab for MRD+ CRC after definitive treatment	Recruiting
BioNTech Vaccine NCT04486378	II	RO7198457 versus watchful waiting in patients with MRD+ stage II/III rectal or colon ca	Not recruiting
MRD-GI NCT05482516	II	Atezolizumab and bevacizumab. Non-randomized, open-label, multi-cohort, multi-site study for pts MRD+ GI ca after definitive treatment	Recruiting
AmMAX CSF1R NCT06617858	II	AMB-05X (CSF1R) in patients with CRC MRD as determined by a ctDNA(+) blood test and no clinically detectable radiographic disease	Recruiting

Clinical Trials for MRD+ CRC (US)

Targeted therapy and chemotherapy trials

Source: https://crcmrd.com/

Name	Phase	Description	Enrollment
NCT04920032	Ib	TAS-102 + irinotecan in patients with MRD+ colon cancer	Recruiting
NCT05343013	II	TAS-102 +/- celecoxib in patients with MRD+ colorectal cancer	Recruiting
NCT07023289	II	Telisotuzumab adizutecan alone or with SOC in participants with post adjuvant MRD+ CRC and no radiographic disease	Recruiting
SU2C NCT03803553	II	Comparison of active surveillance, FOLFIRI or molecularly guided treatment nivolumab (MSI-H), encorafenib/ binimetinib/ cetuximab (BRAF V600E), trastuzumab + pertuzumab (HER2+) for MRD+ CRC	Recruiting
REACT-CLM NCT05062317	II	Risk-stratified adjuvant therapy for patients with MRD+ disease after resection colorectal liver metastases	Recruiting
Precision-MRD NCT06878131	II	Observational study of pts with MRD+ CRC receiving SOC biomarker-directed therapy (BRAF, KRAS G12C, MSI-H, HER2)	Recruiting

QUESTIONS?

We are taking a short break!

The program will resume at 10:50 AM ET

Up Next…

Drs Jonathan Goldman and Zofia Piotrowska discuss the management of EGFR-mutated non-small cell lung cancer

RTP
RESEARCH TO PRACTICE