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Overcoming Cancer.™

Master Lecture on Endocrine Therapy in Early/Advanced Breast Cancer

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Updates in Oncology from the Masters

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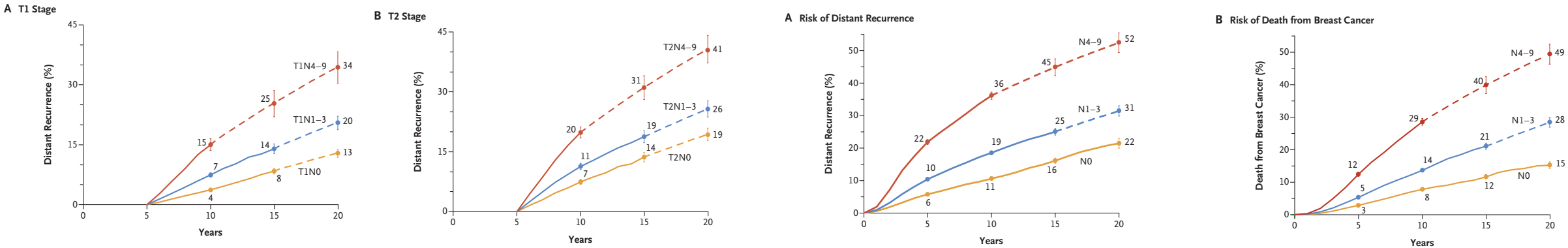
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

- **Meta-analysis of 88 Trials**
- **62,923 women with ER+**
- **ET for 5 years**
- **Disease Free for 5 years**

20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

Hongchao Pan, Ph.D., Richard Gray, M.Sc., Jeremy Braybrooke, B.M., Ph.D., Christina Davies, B.M., B.Ch., Carolyn Taylor, B.M., B.Ch., Ph.D., Paul McGale, Ph.D., Richard Peto, F.R.S., Kathleen I. Pritchard, M.D., Jonas Bergh, M.D., Ph.D., Mitch Dowsett, Ph.D., and Daniel F. Hayes, M.D., for the EBCTCG*

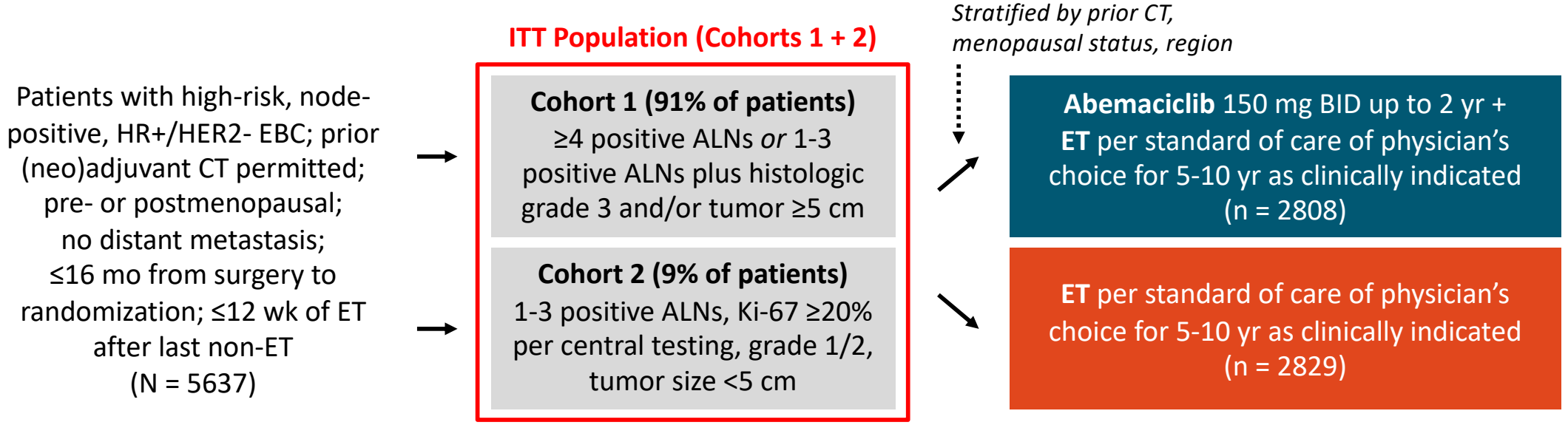


- **After 5 years of adjuvant ET, distant recurrences occurred steadily for at least another 15 years.**
- **Small node negative (T1N0), low-grade tumors the risk of distant recurrence is 10% during years 5 to 20.**
- **There was a strong association of tumor grade and Ki-67 with the risk of recurrence during years 0 to 5 but moderate association during years 5 to 20. Same with tumors with PgR negative.**

Pan H, et al, NEJM 2017.

MonarchE: Abemaciclib combined with ET for the adjuvant treatment of HR+, HER2-, Node-positive, EBC

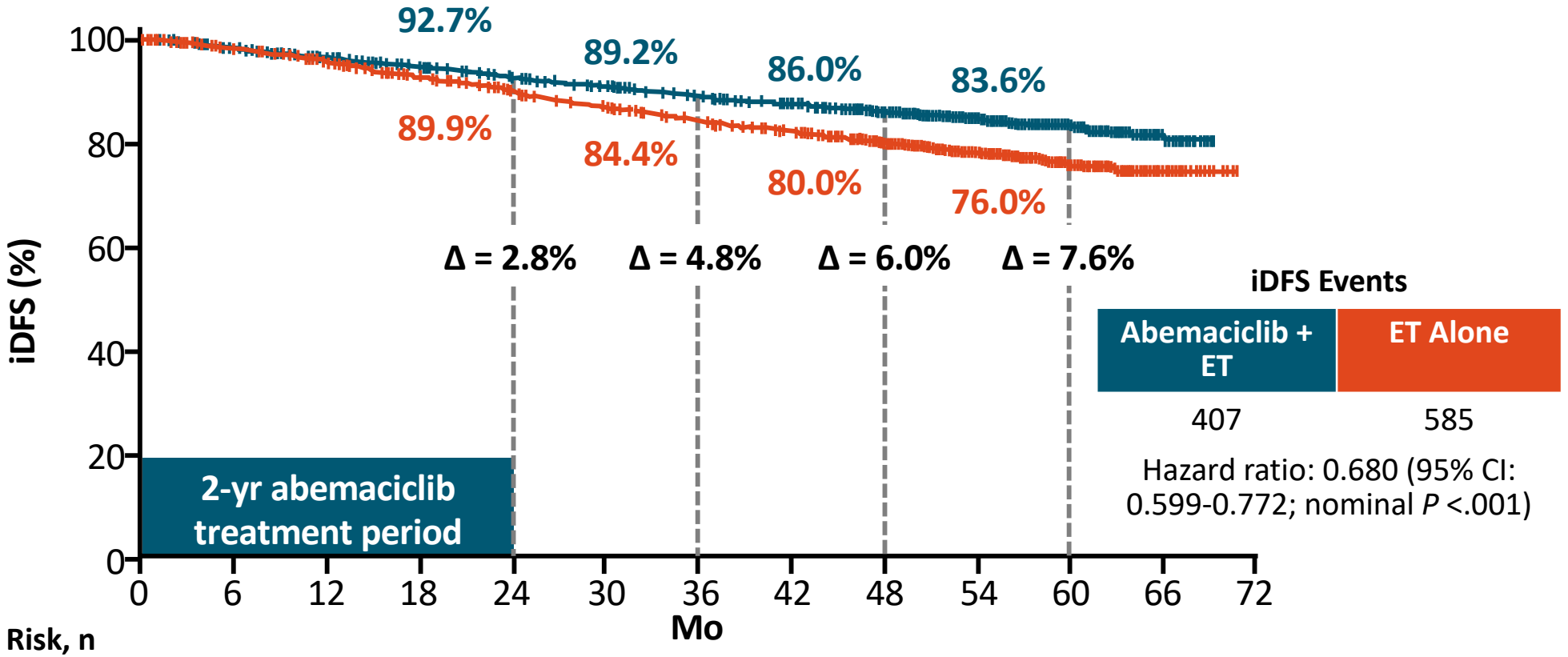
- International, randomized, open-label phase III trial



- **Primary endpoint:** iDFS
- **Key secondary endpoints:** iDFS in Ki-67 high (≥20%) population, DRFS, OS, safety, PROs
- Median follow-up for analysis presented at OS IA3 (data cutoff: July 3, 2023): 4.5 yr (54 mo)
  - All patients off abemaciclib and >80% followed for ≥2 yr since completing abemaciclib

Johnston SRD, JCO 2020; Harbeck S, et al ESMO 2023, Abstr. LBA17.

MonarchE: iDF in ITT Population at Median Follow-up of 4.5 Yr



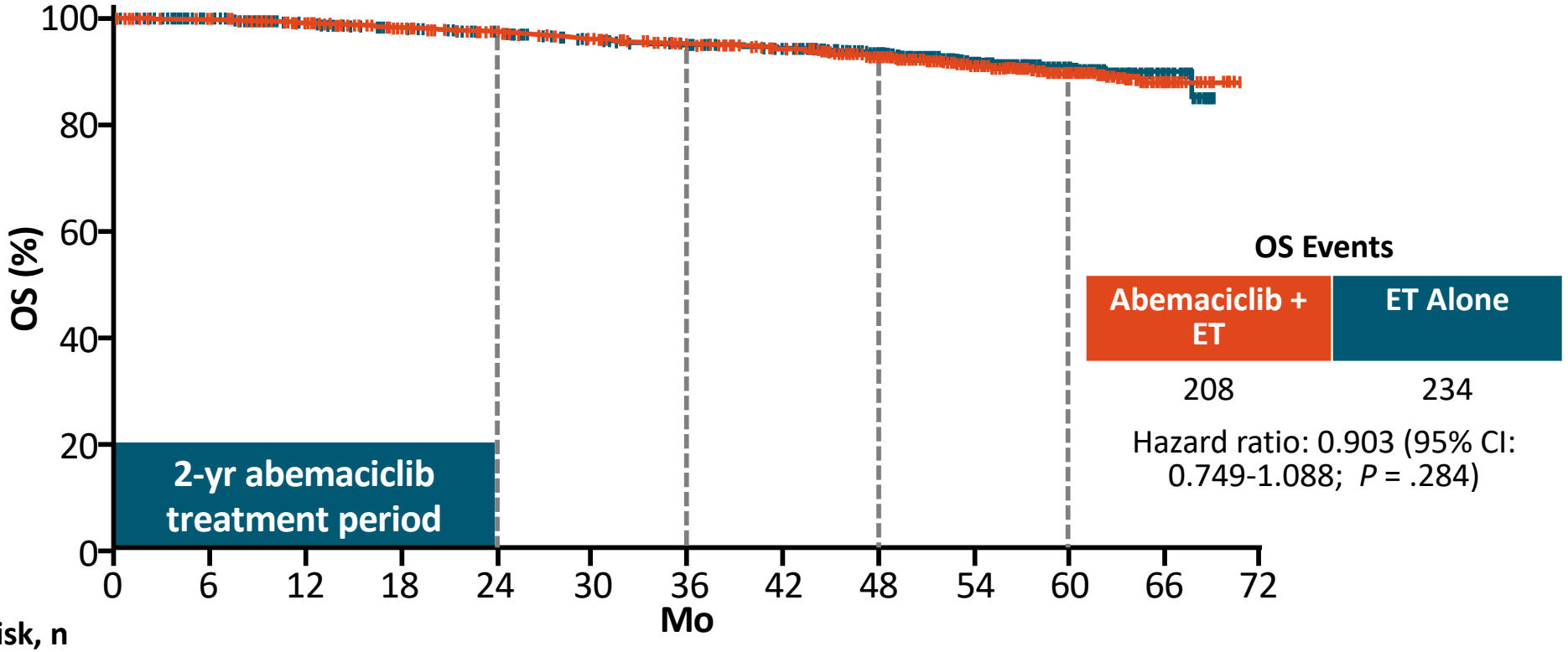
Patients at Risk, n

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

Consistent benefit across all patient and disease subgroups, independent of Ki-67 index

Harbeck N, et al. ESMO 2023. Abstr LBA17.

MonarchE: OS in ITT Population at Median Follow-up of 4.5 Yr.



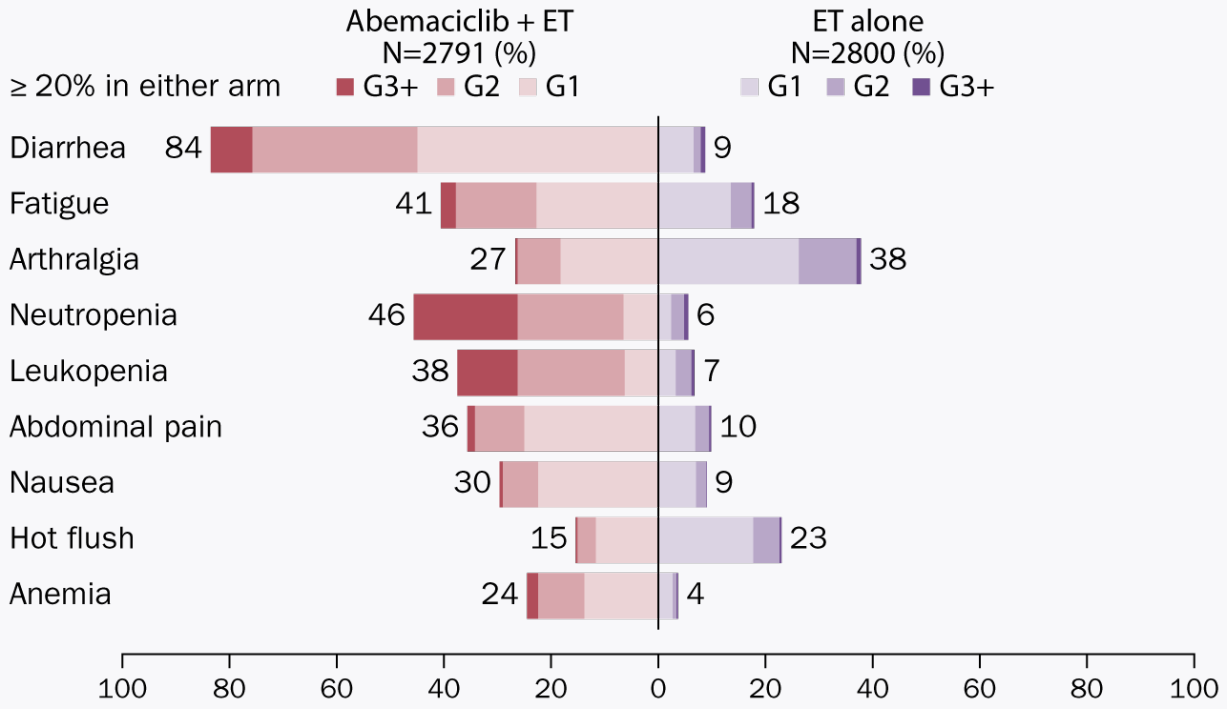
Patients at Risk, n													
Abemaciclib + ET	2808	2666	2614	2566	2518	2455	2407	2373	2260	1271	528	80	0
ET alone	2829	2705	2664	2599	2545	2496	2440	2382	2243	1279	538	77	0

No statistically significant difference in OS; numerically fewer deaths with abemaciclib

Harbeck N, et al. ESMO 2023. Abstr LBA17.

MonarchE: Safety Summary

AEs ≥20% in Both Treatment Arms[2]



Among the 2304 patients who experienced diarrhea[3]

- Median time to onset (any grade) was 8 days
- 20.5% had ≥1 dose reduction
- 22.9% had dose holds
- 5.0% of patients had their treatment discontinued

Other events of interest,[2] any grade	Abemaciclib + ET (n=2791)	ET alone (n=2800)
VTE, %	2.5	0.6
PE, %	1.0	0.1
ILD, %	3.2	1.3

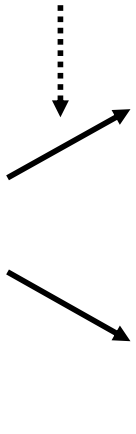
Johnston SRD, JCO 2020.

NATALEE: Adjuvant Ribociclib plus ET in Intermediate- to High-risk HR+/HER2- EBC

- International, randomized, open-label phase III trial

Stratified by stage (II vs III), menopausal status (men and premenopausal vs postmenopausal women), prior (neo)adjuvant CT (yes vs no), geography (N America/W Europe/Oceania vs rest of world)

Pre/postmenopausal women and men with HR+/HER2- EBC; stage IIA (either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1, stage IIB (N0 or N1), or stage III disease; prior ET up to 12 mo permitted; prior (neo)adjuvant CT permitted (N = 5101)



Ribociclib 400 mg PO QD for 3 wk on/1 wk off for 3 yr + **NSAI*** for ≥5 yr (n = 2549)

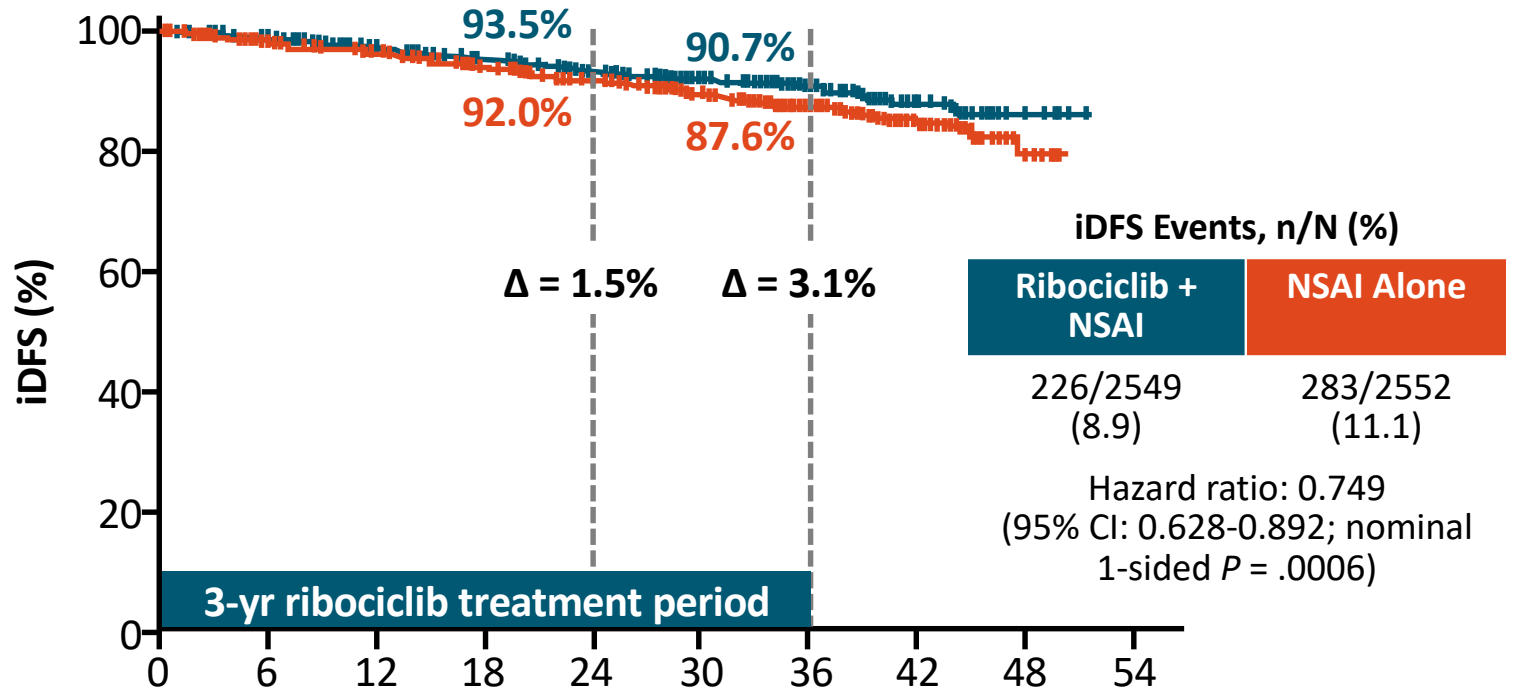
NSAI* for ≥5 yr (n = 2552)

*Letrozole or anastrozole. Men and premenopausal women also received goserelin 3.6 mg/28 d.

- **Primary endpoint:** iDFS (STEEP criteria)
- **Key secondary endpoints:** recurrence-free survival, DDFS, OS, PROs, PK, safety
- Median follow-up for final protocol-specified iDFS analysis: 33.3 mo (data cutoff: July 21, 2023)

Hortobagyi G, et al, SABCS 2023; Slamon ASCO 2023. Abst LBA500.

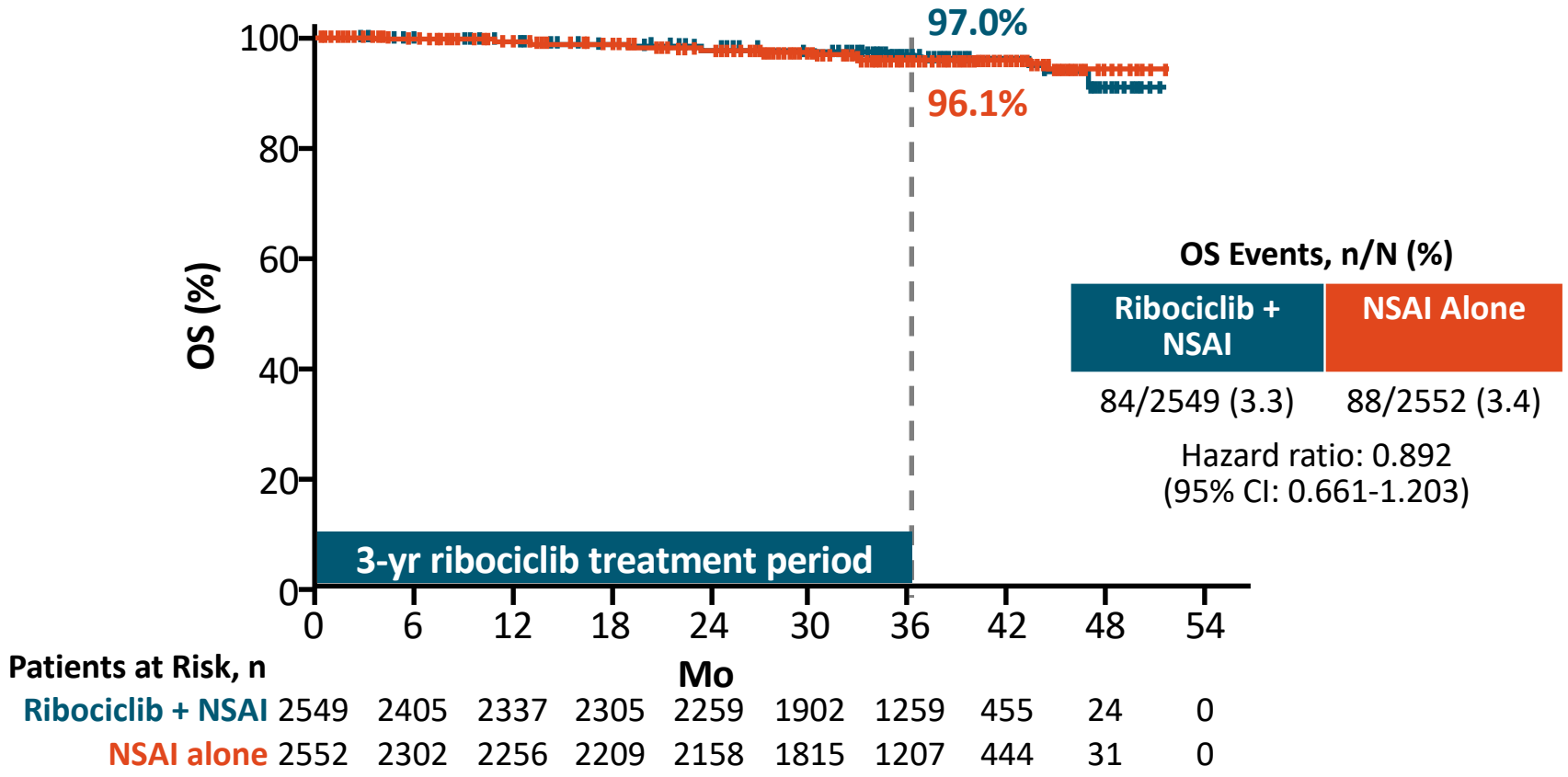
NATALEE: Final iDFS Analysis at Median Follow-up at 33.3 Months



Ribociclib + NSAI significantly reduced risk of invasive disease by 25.1% vs NSAI alone (*P* = .0006)

Hortobagyi G, et al, SABCS 2023, Abstr GS03-03.

NATALEE: OS at Median Follow-up at 35.9 Mo



OS data immature (events in <4% at time of analysis)

Hortobagyi G, et al, SABCS 2023, Abstr GS03-03.

NATALEE: Safety With Adjuvant Ribociclib + ET

AEs of Special Interest, %[1]	Ribociclib + NSAI (n = 2525)		NSAI Alone (n = 2442)	
	Any	Gr ≥3	Any	Gr ≥3
Neutropenia	62.5	44.3	4.6	0.9
▪ Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs	26.4	8.6	11.2	1.7
QT interval prolongation	5.3	1.0	1.4	0.6
▪ ECG QT prolonged	4.3	0.3	0.7	0
ILD/pneumonitis	1.5	0	0.9	0.1

Other Clinically Relevant AEs, %[1]	Ribociclib + NSAI (n = 2525)		NSAI Alone (n = 2442)	
	Any	Gr ≥3	Any	Gr ≥3
Arthralgia	37.3	1.0	43.3	1.3
Nausea	23.0	0.2	7.8	0.0
Headache	22.8	0.4	17.0	0.2
Fatigue	22.3	0.8	13.2	0.2
Diarrhea	14.5	0.6	5.5	0.1
VTE	1.5	0.6	0.8	0.4

- Ribociclib 400 mg had lower rates of dose-dependent toxicities vs pooled analysis of MONALEESA trials using ribociclib 600 mg for advanced disease[2]
  - Neutropenia: 62% vs 74%; ECG QT prolongation: 4.2% vs 6.5% (grade ≥3: 0.2% vs 1.2%)

Hortobagyi G, et al, SABCS 2023, Abstr GS03-03.

Who May Benefit From Adjuvant Treatment with CDK4/6 inhibitors for HR+/HER2- EBC?

Eligible | Eligible if meet additional criteria | Ineligible

AJCC Anatomical Staging	TN (M0)	NATALEE: Ribociclib	monarchE: Abemaciclib
IA	T1N0		
IB	T0N1mi		
	T1N1mi		G3 or Ki67 ≥20%
IIA	T0N1		
	T1N1		G3 or Ki67 ≥20%
	T2N0	G3, or G2 with Ki-67 ≥20% or high genomic risk*	
IIB	T2N1		G3 or Ki67 ≥20%
	T3N0		
IIIA	T0N2		
	T1N2		
	T2N2		
	T3N1		
	T3N2		
IIIB	T4N0		
	T4N1		
	T4N2		
IIIC	Any TN3		

- Pre/postmenopausal women
- Men
- **Tx choice depends on:**
  - Approval
  - Access
  - Risk
  - Long-term efficacy
  - Safety profile
  - Patient preference
- **Do not forget to test for g*BRCA*m** – determines eligibility for adjuvant olaparib (OlympiA)

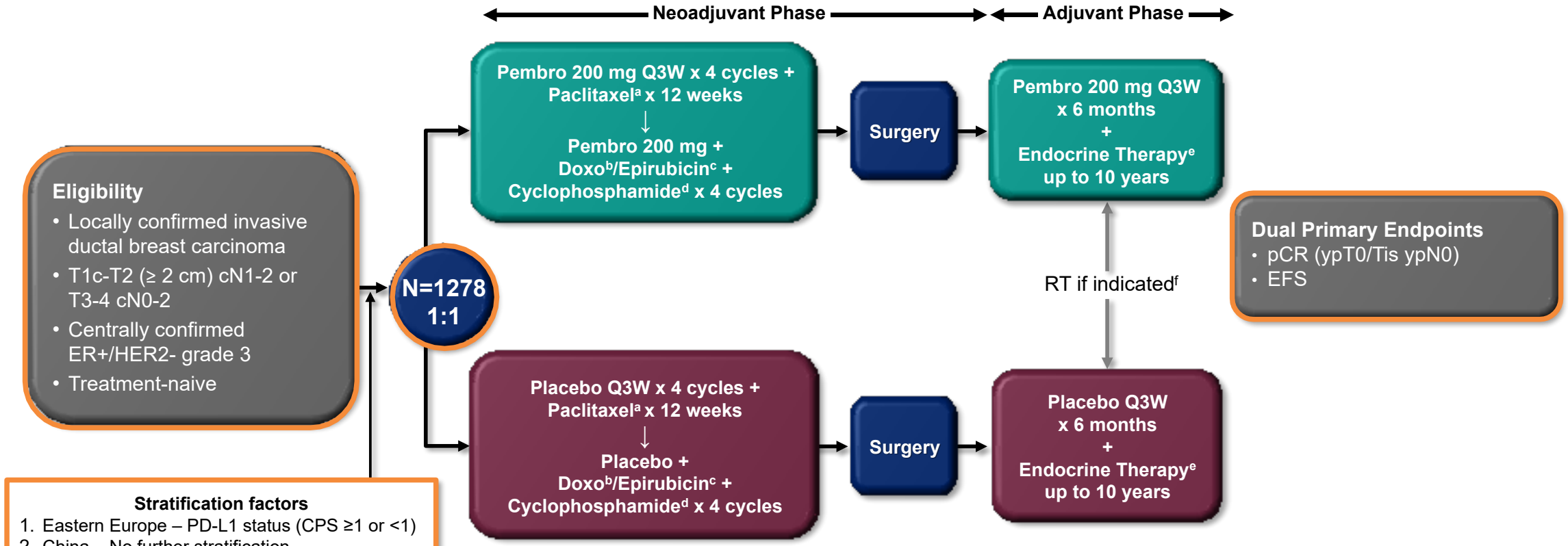
*According to Oncotype DX, Prosigna PAM50, or EndoPredict EPclin Risk Score.

Herbert N, ASCO 2023..

Conclusions: Adjuvant CDK4/6 Inhibitors for Patients With HR+/HER2- EBC

- Recurrence is a concern for patients with HR+/HER2- early breast cancer, especially those with high-risk features
- Risk of recurrence is decreased with:
  - Adjuvant abemaciclib for high-risk, node-positive disease
  - Adjuvant ribociclib for intermediate-/high-risk disease
- AEs associated with adjuvant CDK4/6 inhibitors can be effectively managed with supportive care and dose reductions
- FDA approval and guidelines recommend use of abemaciclib in ITT population on monarchE trial—not limited to those with Ki-67 ≥20%

Keynote-756: Phase III study of PST Pembrolizumab or Placebo plus Chemotherapy in HR EBC



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

O'Shaughnessy J, et al. SABCS 2023.

CheckMate 7FL: Phase III study of PST Nivolumab or Placebo plus Chemotherapy in HR EBC

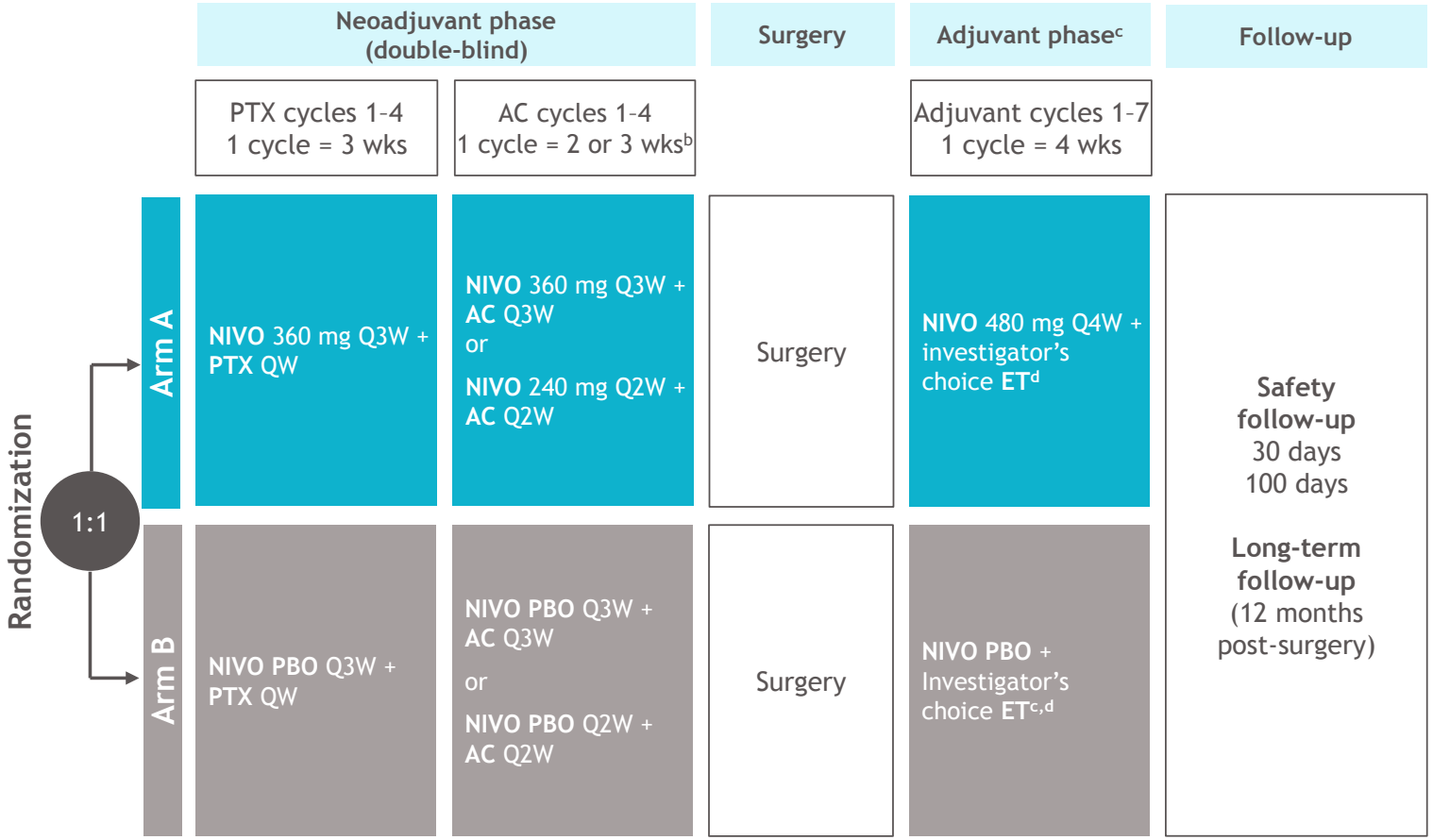
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c (tumor size 2 cm only)-T2, cN1–cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1–10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0–1

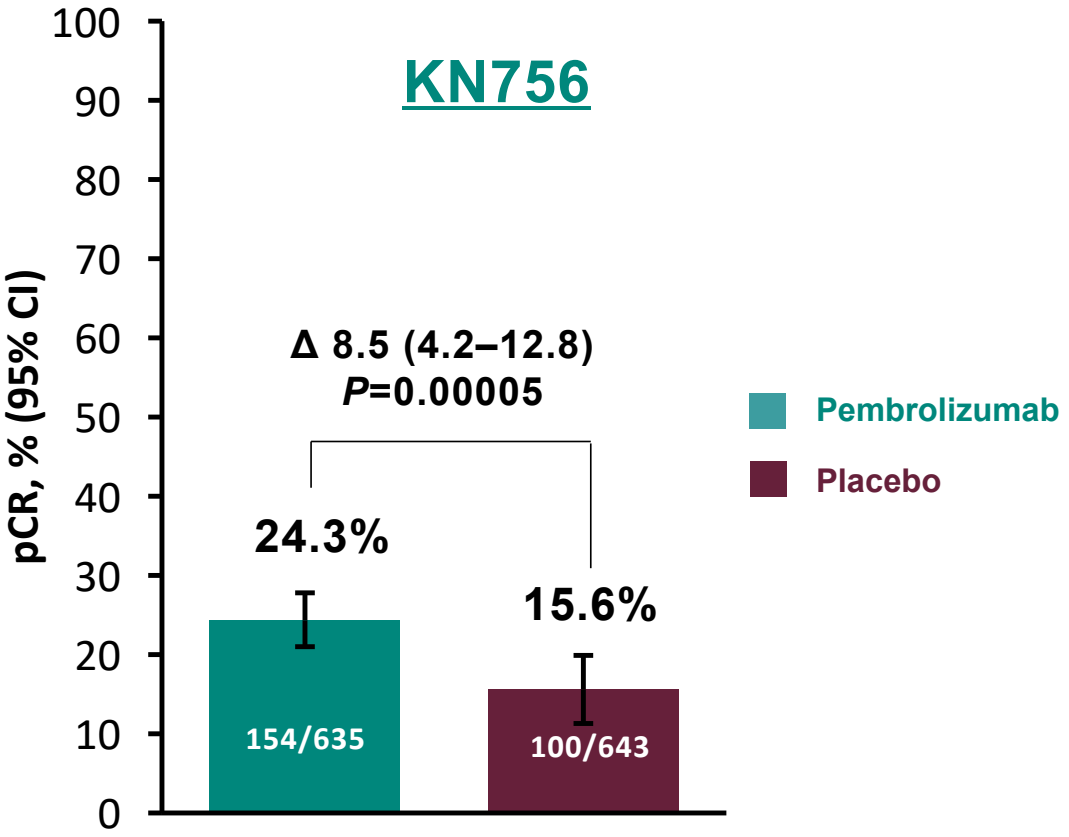
Stratification factors

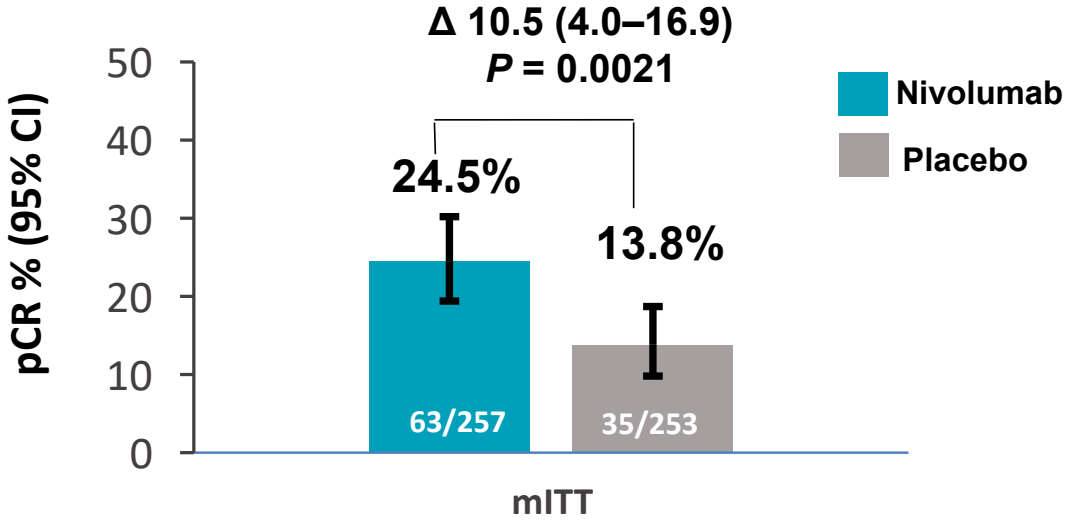
- PD-L1 IC (≥ 1% or < 1%) by SP142
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



Loi, S, et al. SABCS 2023.

Primary End Point: pCR





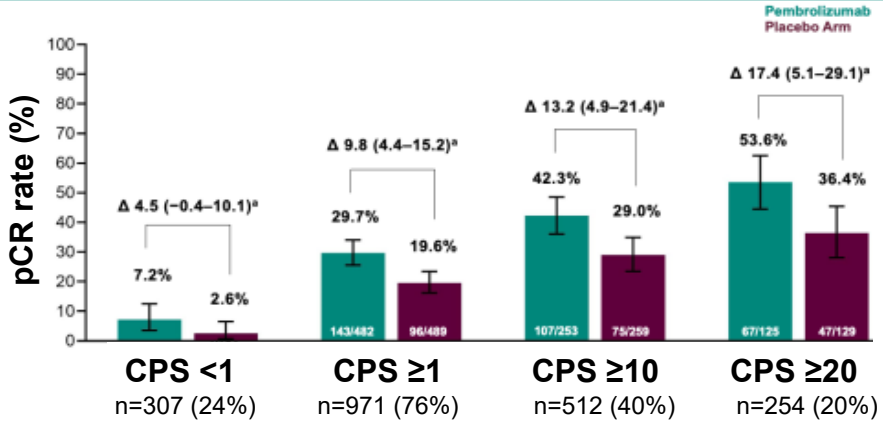
Loi, S, et al. SABCS 2023. O'Shaughnessy J, et al. SABCS 2023.

Keynote 756: Key Subgroup and Biomarker Analysis

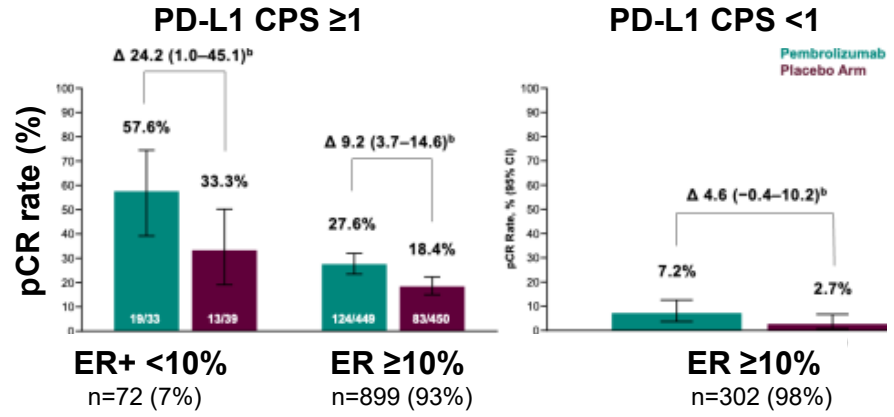
Clinical charact.	Impact of pembro on pCR rate
Stage II (n-807) III (n=471)	• Benefit regardless of stage - stage II (+Δ 9.1) and III (+Δ 8.0)
LN involvement pos (n=1152) neg (n=126)	• Benefit in LN pos (+Δ 9.3) • Benefit less clear LN neg (+Δ3.8)
Chemo exposure full (n=634) partial (n=641)	• Benefit regardless of whether chemotherapy completed

Biomarker	Impact of pembro on pCR rate
PD-L1 22C3 CPS	• Benefit if CPS ≥1. Higher pCR rates & larger Δ with higher CPS • Benefit less clear CPS <1
ER status Stratified by CPS score	• CPS ≥1: Benefit for all ER%, with larger benefit if ER <10% • CPS <1: Benefit less clear ER ≥10%

PD-L1 status (22C3 CPS)



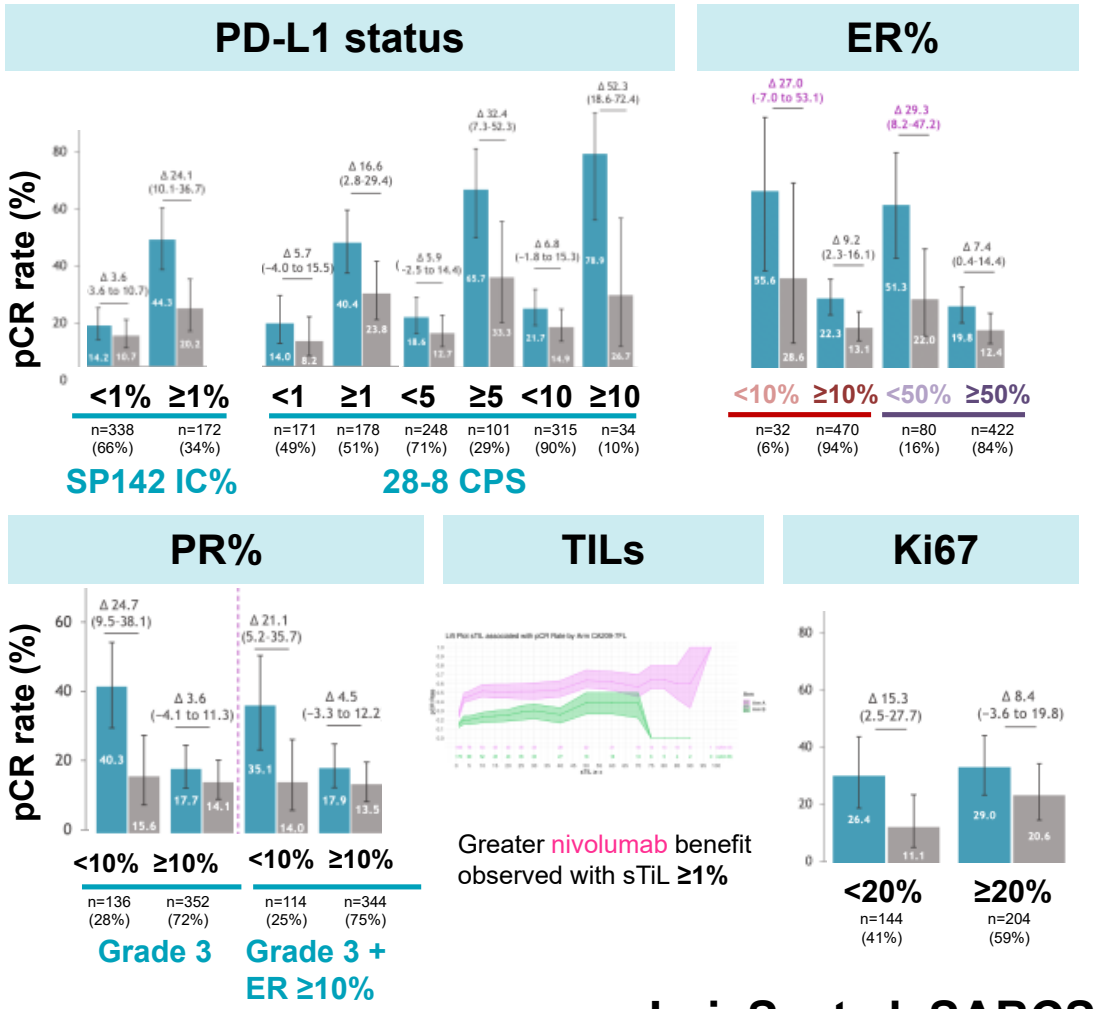
ER status



O'Shaughnessy J, et al. SABCS 2023.

Checkmate-7FL: Biomarkers Predictive of pCR or RCB 0/1

Biomarker	Impact of nivo on pCR and RCB 0/1 rates
PD-L1 score SP142 IC% (n=510) 28-8 CPS (n=349)	• Benefit if PD-L1+ by both assays, with increasing benefit in higher 28-8 CPS scores • Benefit less clear PD-L1 neg
ER%	• Benefit with low ER% (<50%) • Benefit less clear high ER% (≥50%)
PR% Stratified by ER	• Benefit with low PR% (<10%) • Benefit less clear high PR% (≥10%)
sTIL (<5%, ≥5%)	• Higher with sTIL ≥1% • Benefit less clear sTIL <1%
Ki67 (<20%, ≥20%)	• No association



Loi, S, et al. SABCS 2023.

Conclusions: PST with and without IOs in HR+ HR-BC

Key findings from KN756 and Checkmate-7FL biomarker data:

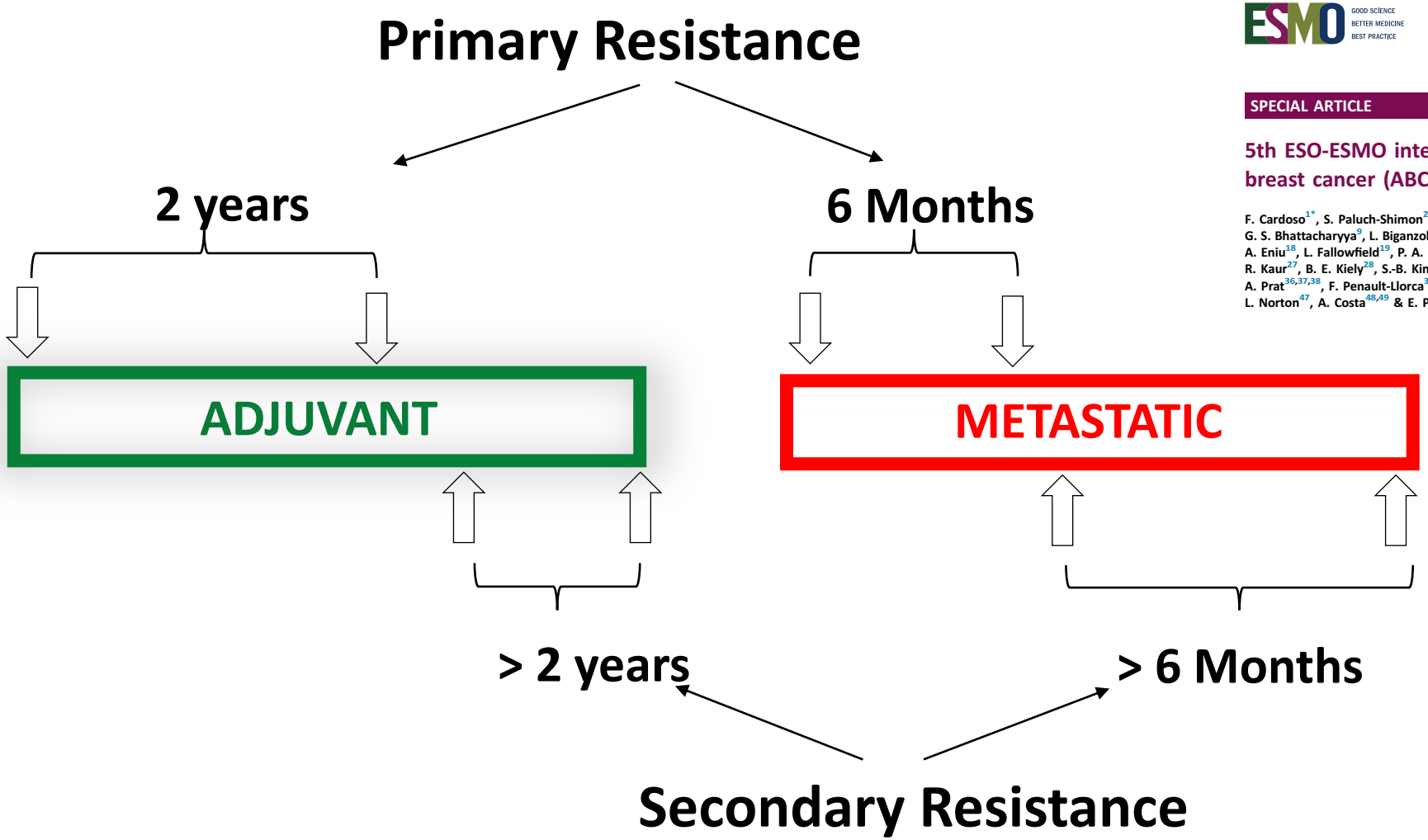
- Neoadjuvant IO in combination with NACT improved pCR rates in high-risk HR+/HER2- early-stage breast cancer, particularly in patients who were:
  - **PD-L1+** (both KN756 and 7FL; especially with higher CPS scores)
  - **Low %ER** (<50% 7FL; if PD-L1+, regardless of ER% <10% or ≥10% in KN756)
  - **Low %PR** (7FL)
  - **Low sTILs** (≥1%) (7FL)

Future steps:

- Await EFS data!
- How do these biomarkers correlate with EFS data?
- Response by sTIL in KN756? Response in the PD-L1 subgroup over the full continuum of ER % positivity?
- Should biomarker(s) be used to help allocate IO for patients with HR+/HER2- EBC? Can we identify an optimal composite biomarker of IO response?

GOAL = Balance efficacy with potential toxicity and help individualize care!!

Breast Cancer: HR+ ET Resistance Definitions



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)☆

F. Cardoso[1*], S. Paluch-Shimon[2], E. Senkus[3], G. Curigliano[4], M. S. Aapro[5], F. André[6], C. H. Barrios[7], J. Bergh[8], G. S. Bhattacharyya[9], L. Biganzoli[10], F. Boyle[11], M.-J. Cardoso[1,12], L. A. Carey[13], J. Cortés[14,15], N. S. El Saghir[16], M. Elzayat[17], A. Eniu[18], L. Fallowfield[19], P. A. Francis[20], K. Gelmon[21], J. Gligorov[22], R. Haidinger[23], N. Harbeck[24], X. Hu[25], B. Kaufman[26], R. Kaur[27], B. E. Kiely[28], S.-B. Kim[29], N. U. Lin[30], S. A. Mertz[31], S. Neciosup[32], B. V. Offersen[33], S. Ohno[34], O. Pagani[35], A. Prat[36,37,38], F. Penault-Llorca[39,40], H. S. Rugo[41], G. W. Sledge[42], C. Thomssen[43], D. A. Vorobiof[44], T. Wiseman[45], B. Xu[46], L. Norton[47], A. Costa[48,49] & E. P. Winer[30]

67% CONSENSUS

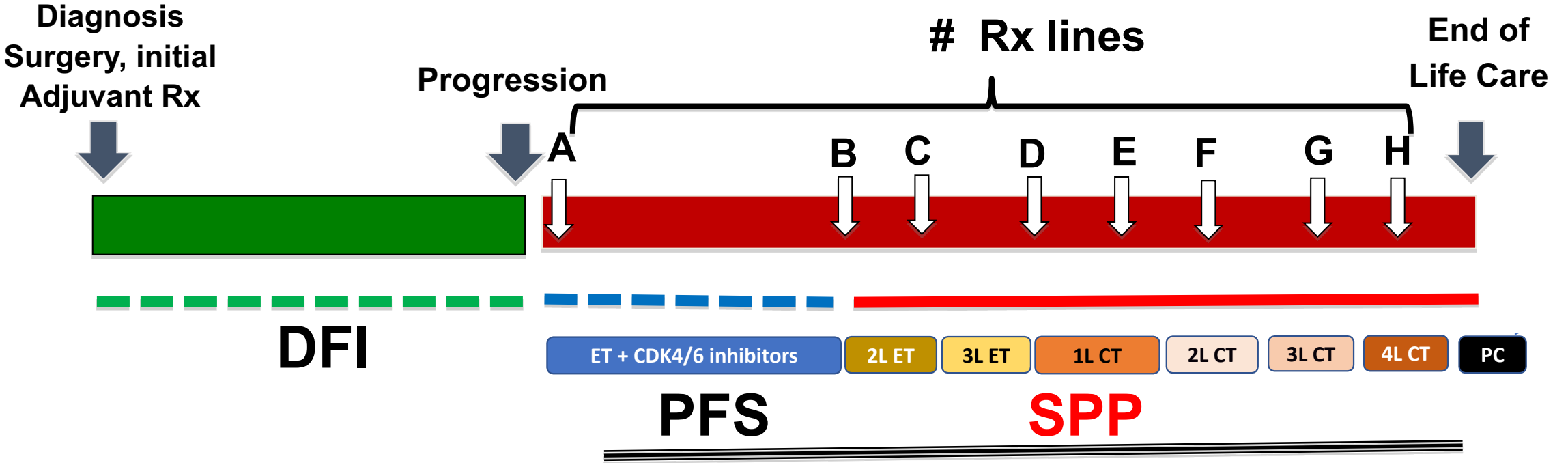
Cardoso F, et al. The Breast 2020.

Current Approach to Newly Diagnosed HR+/HER2-MBC

	PALOMA-2 (N=666)	MONALEESA-2 (N=668)	MONALEESA-3 (N=365)	MONALEESA-7 (N=672)	MONARCH-3 (N=493)
Endocrine Partner	Letrozole	Letrozole	Fulvestrant	Letrozole, Anastrozole, or Tamoxifen + LHRH ag	Letrozole
CDK 4/6 Inhibitor	Palbociclib	Ribociclib	Ribociclib	Ribociclib	Abemaciclib
Median PFS	27.6 vs. 14.5 (Δ 13.1)	NR vs. 14.7	20.5 vs. 12.8 (Δ 7.7)	23.8 vs. 13.0 (Δ 10.8)	29 vs. 14.8 (Δ 14.2)
Hazard Ratio	0.58	0.56	0.59	0.55	0.53
Median OS	53.9 vs. 51.2	63.9 vs. 51.4	67.6 vs. 51.8	58.7 vs. 48.0	68.8 vs. 53.7
Hazard Ratio	0.956	0.76	0.67	0.76	0.80

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Finn. ASCO 2022. Abstr LBA1003. 4. Hortobagyi. NEJM. 2016;375:1738. 5. Hortobagyi. NEJM. 2022;386:942. 6. Slamon. JCO. 2018;36:2465. 7. Neven. Breast Can Res. 2023;25:103. 8. Tripathy. Lancet Oncol. 2018;19:904. 9. Lu. Clin Cancer Res. 2022;28:851. 10. Goetz. JCO. 2017;35:3638. 11. Goetz. ESMO 2022. Abstr LBA15.

The Treatment Journey for MBC
PFS, OS and SPP (Survival Post Progression)

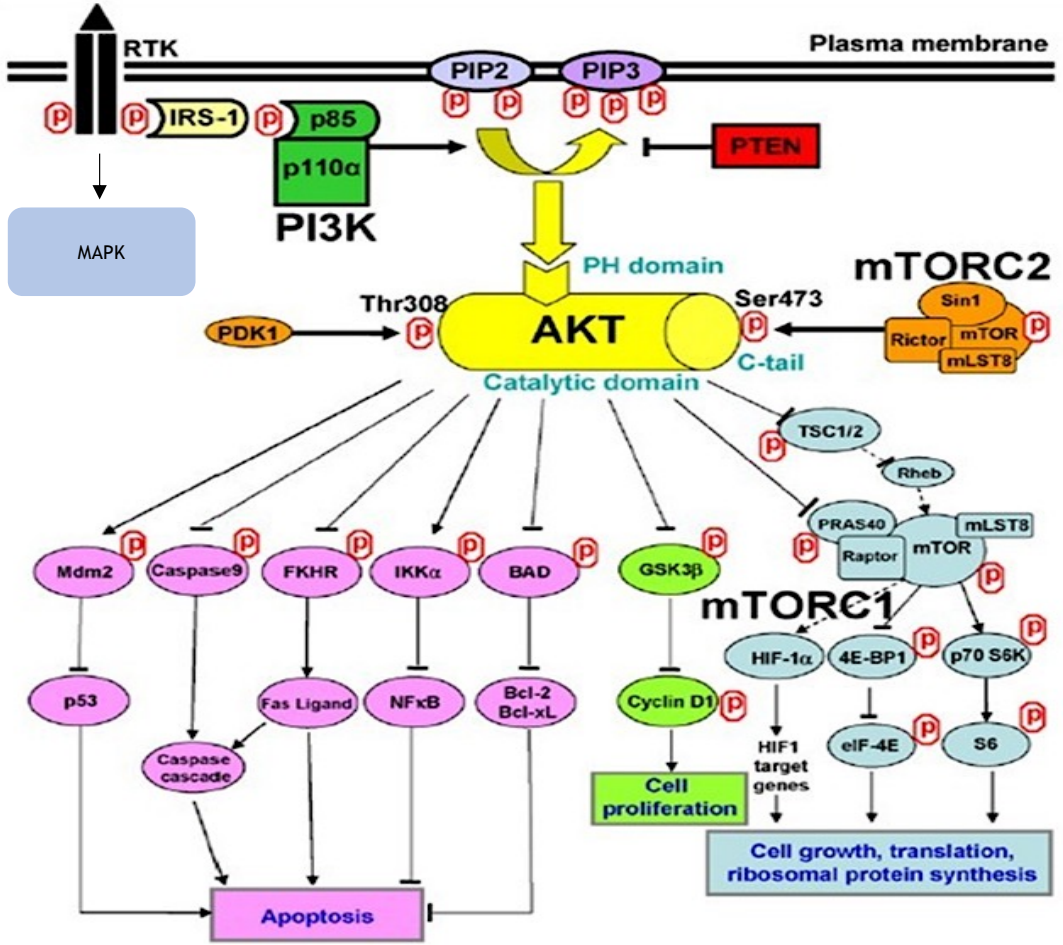


OS = PFS + (OS - PFS)
or OS = PFS + SPP

Strategies post-CDK4/6i

PIK3CAi	New ET agents
SERDs	PARPi
AKTi	CT and ADC

AKT is a Central Node in the *PIK3C/AKT/mTOR* Pathway



Source data: TCGA; except *SU23/PCF Dream Team

Tumour type	PIK3CA mutation (%)	PTEN mutation or loss (%)	AKT1 mutation (%)
Breast	35	11	3
Prostate (metastatic)*	5	40	1
Bladder	22	9	1
Endometrial	53	66	2
Glioblastoma	9	30	<1
Head and Neck	18	2	<1
Lung: squamous	11	18	<1
Gastric-esophageal	5	9	1
Ovarian	<1	6	<1

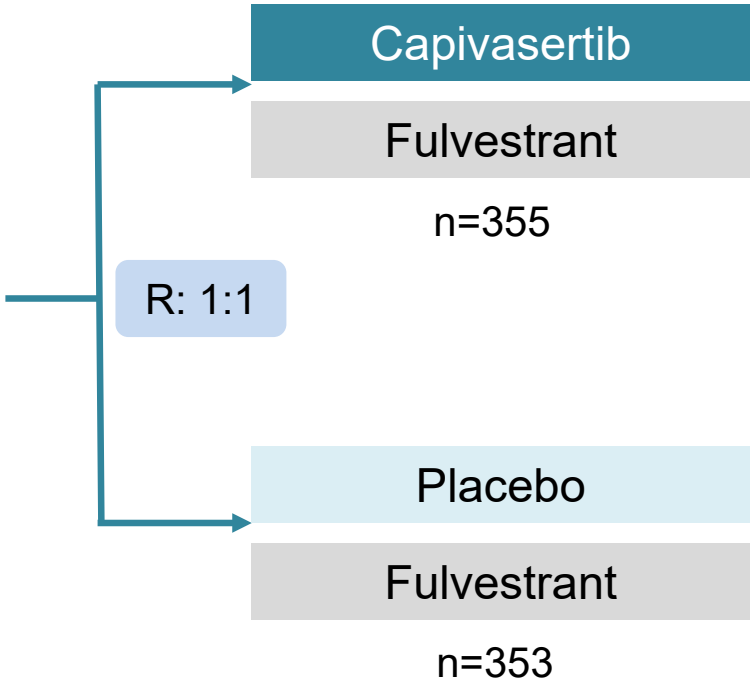
- **AKT is a central node in the PI3K-AKT-mTOR pathway**
- **Pathway activated by multiple mechanisms (tumour-dependent),**
  - **activating mutations in *PIK3CA* (PI3K catalytic sub-unit) and *AKT1*;**
  - **loss of function alterations in *PTEN***
- **AKT activation mediates resistance to inhibitors of RTKs, anti-hormonal agents and chemotherapy**

Yap TA, et al, Curr Op Pharma 2008.

CAPItello-291: Study Design

Adults with HR+/HER2-unresectable or metastatic breast cancer

- Recurrence/progression while on or <12 months from the end of adjuvant AI, or progression on AI in advanced setting
- ≤ 2 lines prior endocrine therapy
- ≤ 1 line chemotherapy
- Prior CDK 4/6 inhibitor in at least 51% of patients
- HbA1c <8% and diabetes not requiring insulin
- FFPE tumor sample from the primary/recurrent cancer available for retrospective testing



Stratification:

- Liver metastases
- Prior CDK 4/6 inhibitors
- Geographic region

Co-Primary endpoints:

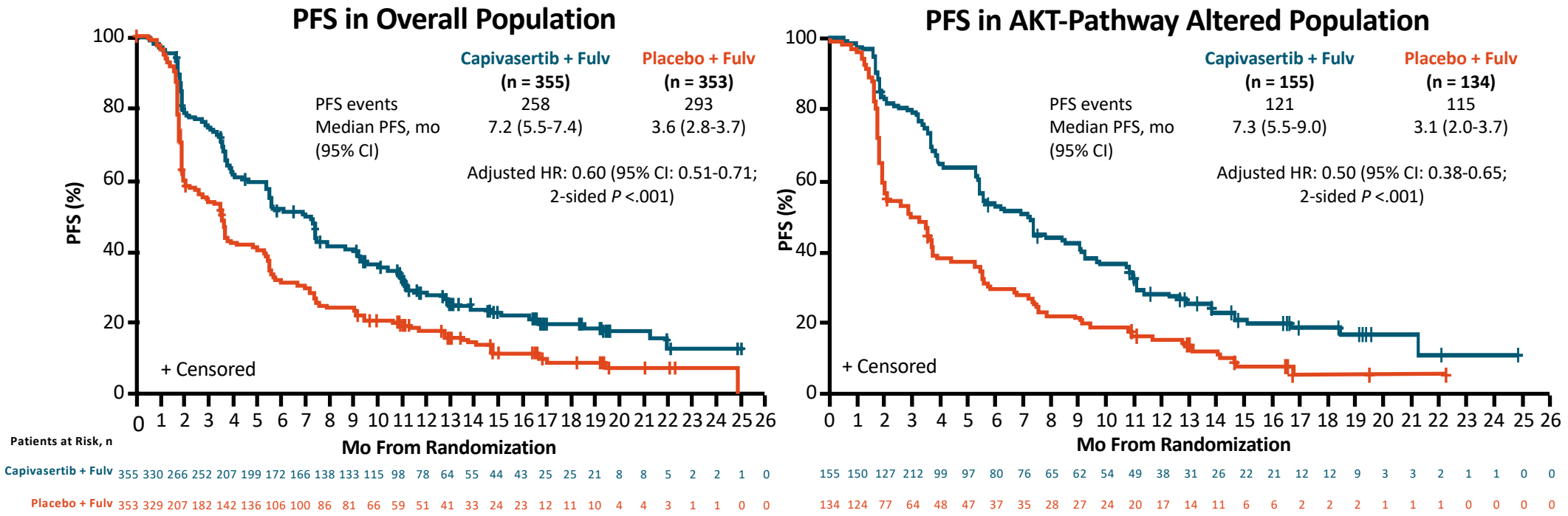
- PFS in overall population; AND
- PIK3CA/AKT1/PTEN-biomarker-pos population

Secondary endpoints:

- OS in overall population
- PIK3CA/AKT1/PTEN-biomarker-pos population
- ORR
- DoR

Turner NC, et al. NEJM 2023.

CAPitello-291: Investigator-Assessed PFS

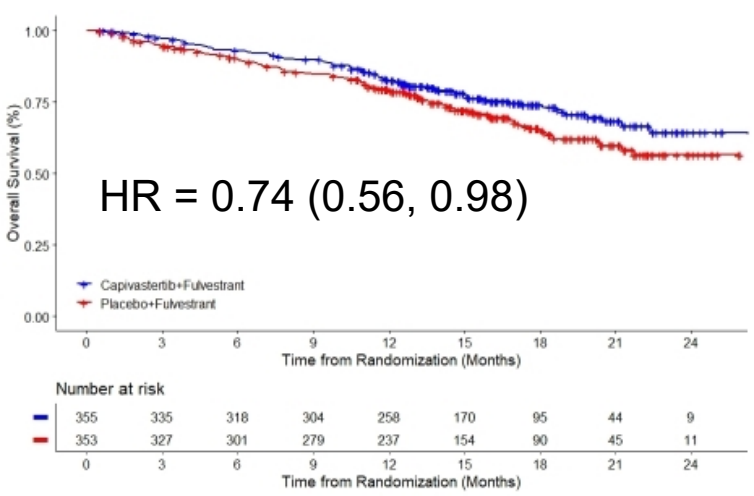


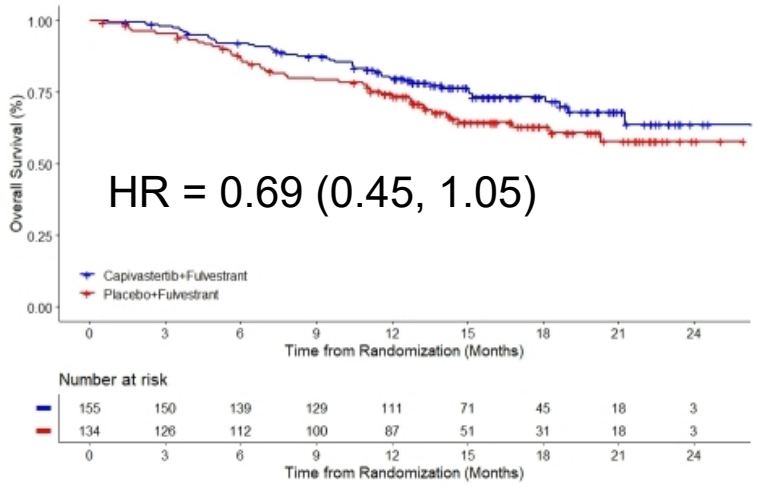
- Study met dual primary endpoints, showing significantly prolonged PFS with capivasertib + Fulv vs placebo + Fulv in overall and AKT pathway–altered populations
- PFS benefit consistent across subgroups, including those with prior CDK4/6 inhibitor and those with liver metastases
- OS data at 28% maturity in overall population; HR: 0.74 in overall population; HR: 0.69 in AKT-altered population

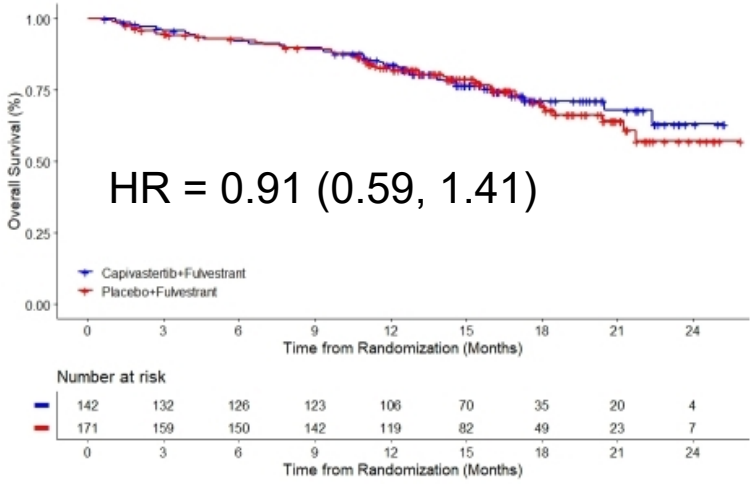
Turner NC, et al. NEJM 2023.

CAPitello-291: OS

Overall N=708	Biomarker-Pos N=289	Biomarker-Neg N=313



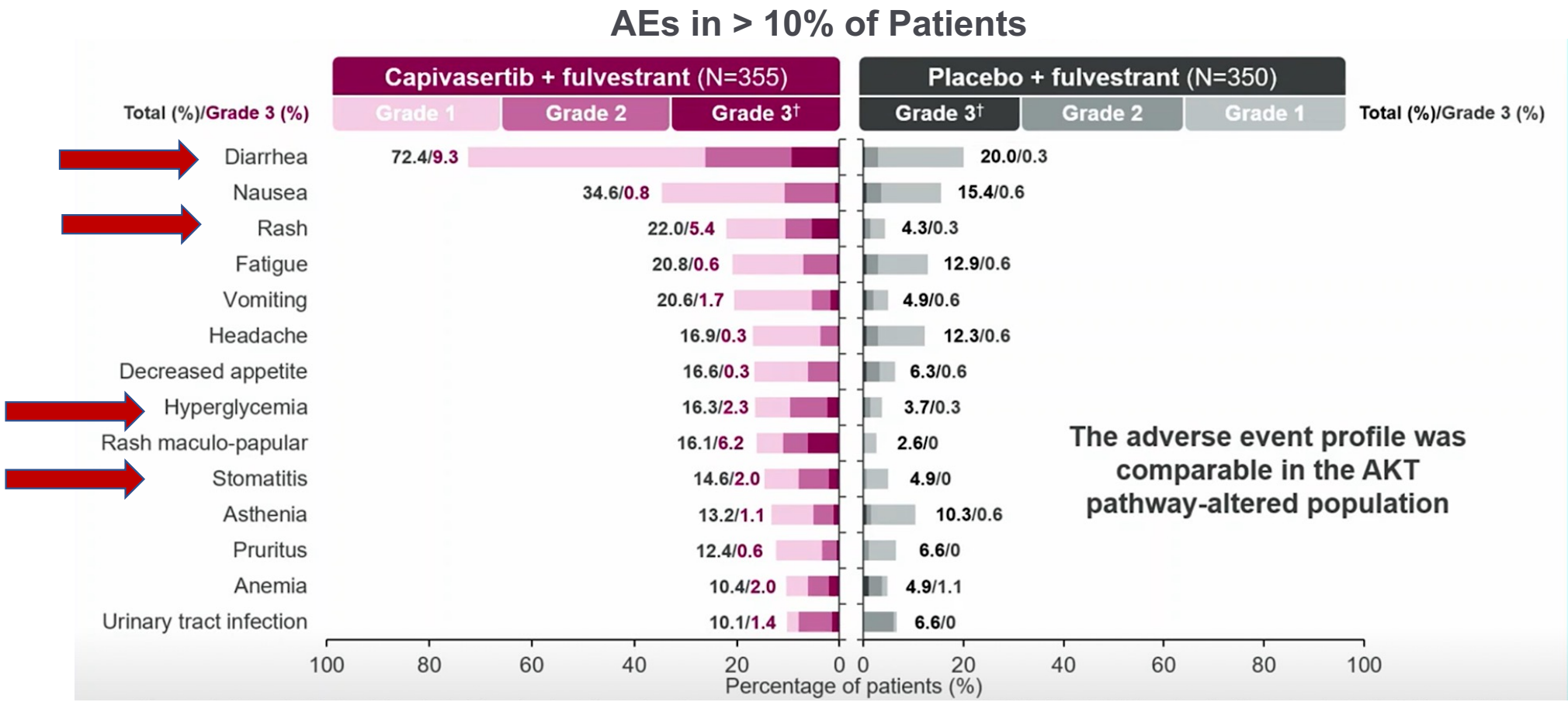




Event #: 87 (25%) vs. 108 (31%) Median = NR (NR, NR) vs NR (21.7, NR)	Event #: 41 (27%) vs. 46 (34%) Median = NR (NR, NR) vs NR (20.3, NR)	Event #: 36 (25%) vs. 46 (27%) Median = NR (22.4, NR) vs. NR (21.3, NR)

Turner NC, et al. NEJM 2023.

CAPitello-291: Adverse Events



35% dose interruption; 20% dose reduction and Discontinuation rate 13%; 9% due to capivasertib

Turner NC, et al. NEJM 2023.

Toxicity Summary: Everolimus, Capivasertib, Alpelisib

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

CAPitello-291: Conclusions

FDA U.S. FOOD & DRUG ADMINISTRATION

- Granted regular approval Nov 16, 2023: In combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA approved test following progression on at least one endocrine based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy
- First approval of an inhibitor of serine/threonine kinase AKT
- Contemporaneous Pre-Market Approval for FoundationOne® CDx

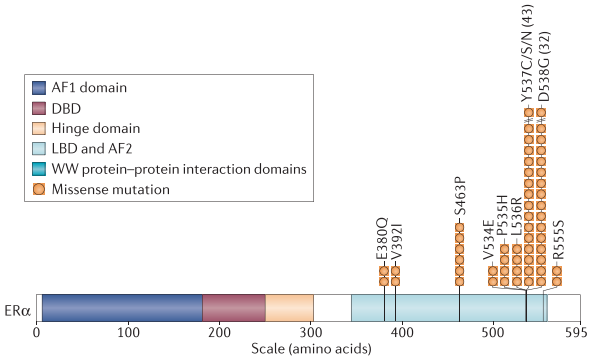
ERS1^{mut} Timeline

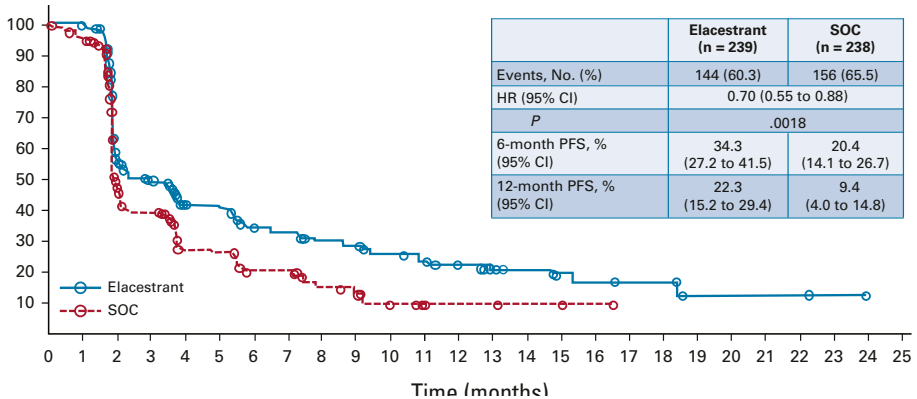
Discovery

Role of *ERS1* In endocrine resistance

First in class *ERS1* antagonist

1997 — **2013** — **2023**





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

Elacestrant
Amcenestrant
Giredestrant
Camizestrant
Imlunestrant

Ma C, et al Nat Rev Cancer 2015; Brett JO, et al. Breast Cancer Res 2021.

EMERALD: Phase III Study of Elacestrant vs. Investigator's Choice

Postmenopausal women or men with ER+HER2- metastatic breast cancer
- 1-2 prior lines of ET
- 1 line ET with a CDK4/6i inhibitor

R: 1:1

Elacestrant
345 mg PO daily

n=239

Investigator's Choice
(AI or fulvestrant)

n=239

Primary endpoint
- PFS per BICR in *ESR1*-mut and ITT

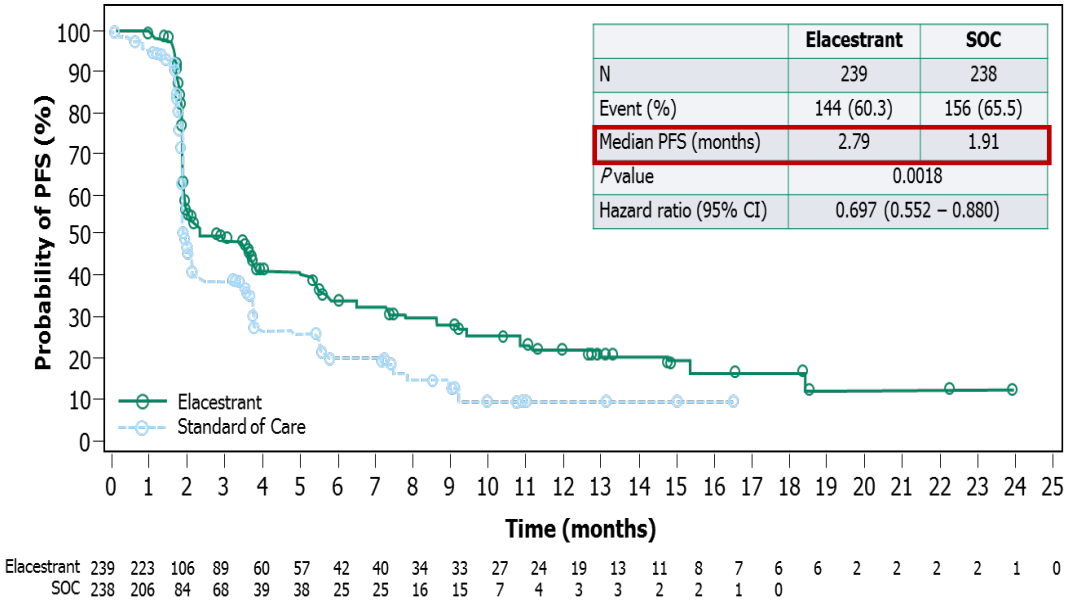
Secondary endpoint
- OS in *ESR1*-mut and ITT

Stratification factors
- *ESR1* mutation(s) (detected or not detected)
- Prior treatment with fulvestrant (yes or no)
- Visceral metastases (yes or no)

Bidart F-C, et al. JCO 2022.

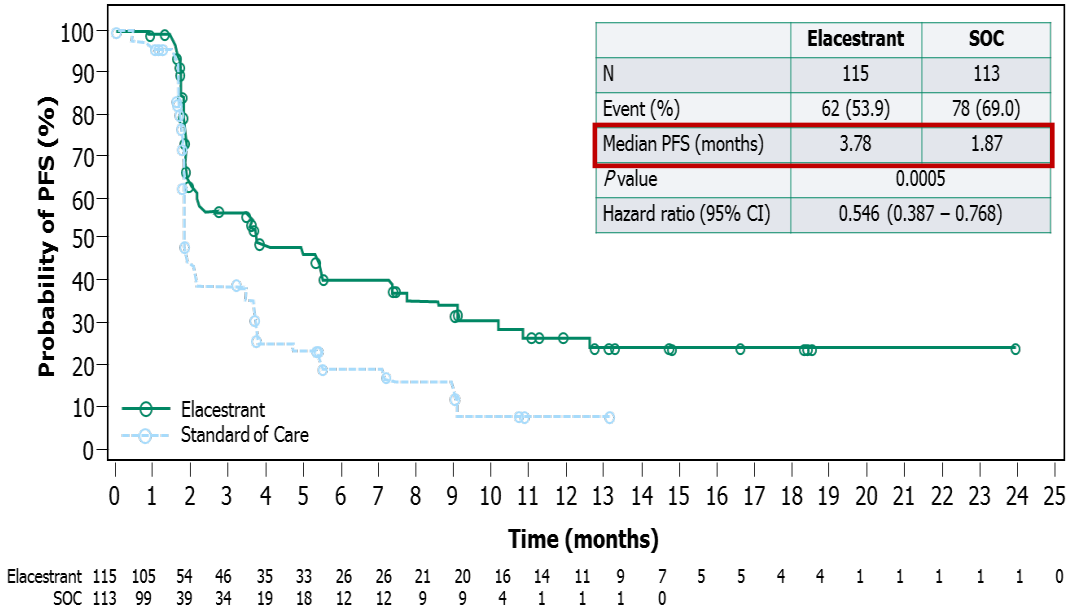
EMERALD: PFS Results

All Patients



	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Patients With Tumors Harboring *mESR1*



	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant is associated with a 30% reduction in the risk of progression or death in all patients with ER+/HER2- MBC

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *mESR1*

Bidart F-C, et al. JCO 2022.

EMERALD: Safety

	Elacestrant % (n=237)	SOC % (n=230)
Treatment-Emergent Adverse Events, All Grade (≥5% Higher with Elacestrant vs. SOC)		
Nausea	35	19
Vomiting	19	9
Decreased Appetite	15	10
Constipation	12	6
Dyspepsia	10	2.6
Laboratory Abnormalities, All Grade (≥5% Higher with Elacestrant vs. SOC)		
Cholesterol Increased	30	17
Triglycerides Increased	27	15
Creatinine Increased	16	6
Hemoglobin Decreased	26	20

Bidart F-C, et al. JCO 2022.

Conclusions

- **Indication restricted to patients with *ESR1* mutations**
  - Trial met PFS endpoint in *ESR1*-mut and ITT, no potential OS detriment
  - PFS improvement in ITT primarily attributable to *ESR1*-mut subgroup
  - Modest PFS improvement in replacement trial may support approval

- **Benefit-risk assessment unfavorable in patients without *ESR1* mutations**
  - Marginally positive PFS trend, uncertainty in OS
  - External data from oral ER antagonists suggest greater activity in *ESR1*-mut

- **Safety**
  - ↑GI toxicity and ↑dyslipidemia

INAVO120: Study Design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Enrolment period: December 2019-September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

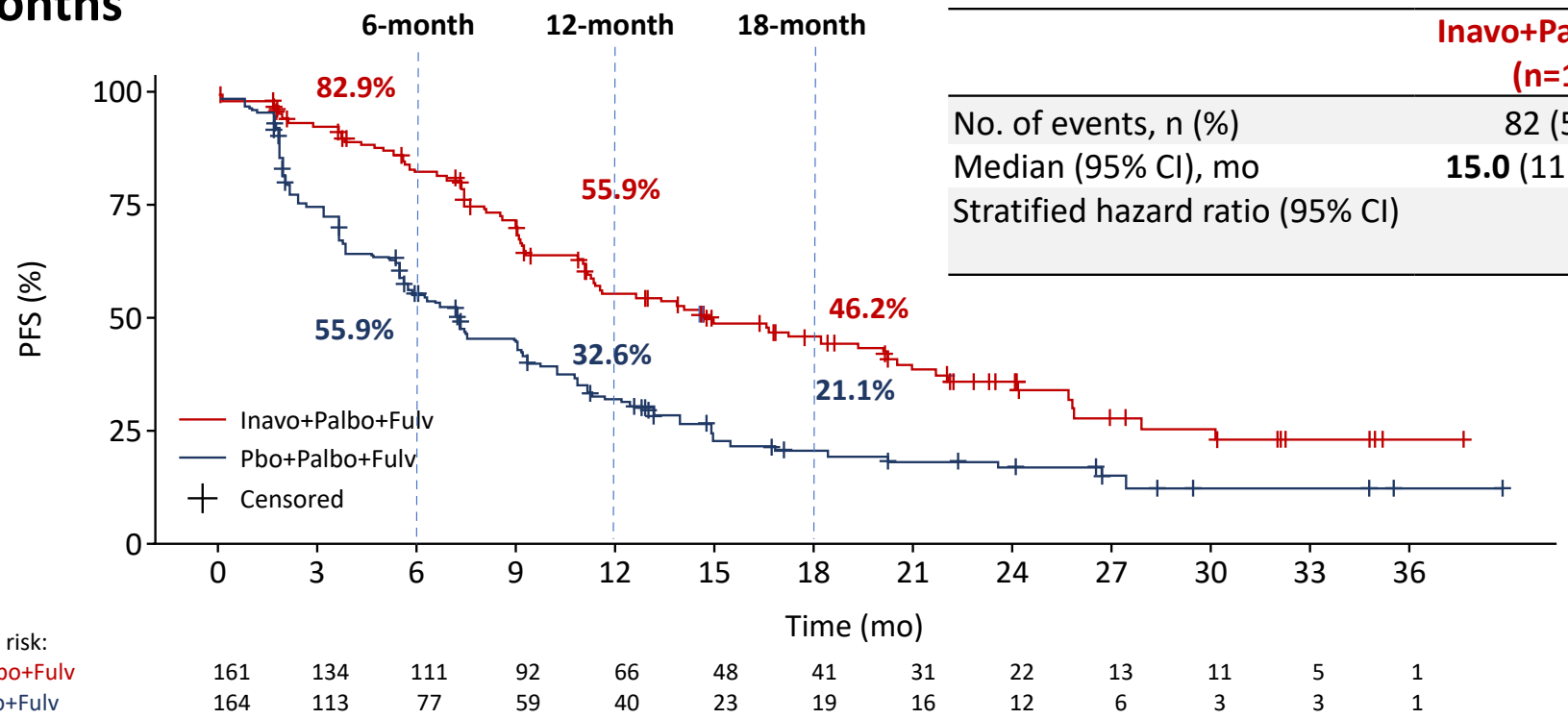
Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

Jhavery K, et al. SABCS 2023.

INAVO120: Investigator-Assessed PFS

Median follow-up: **21.3 months**



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

Patients at risk:

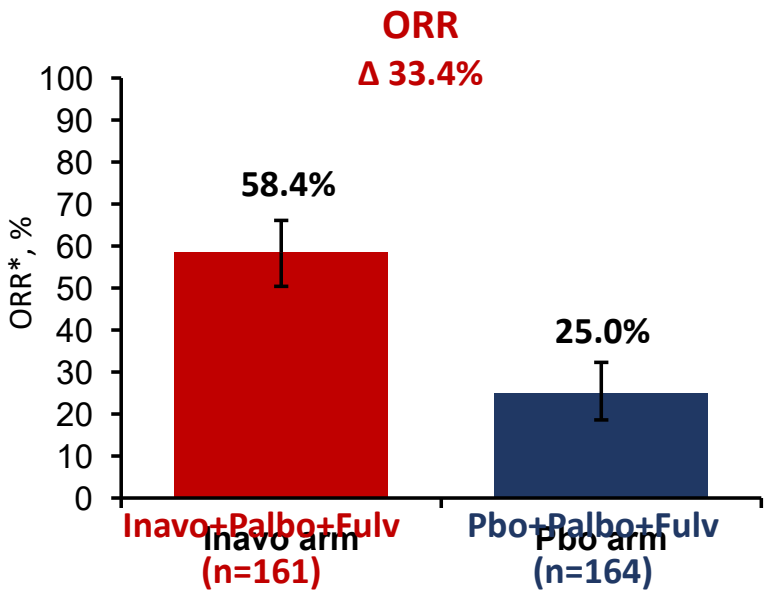
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

CCOD: 29th September 2023

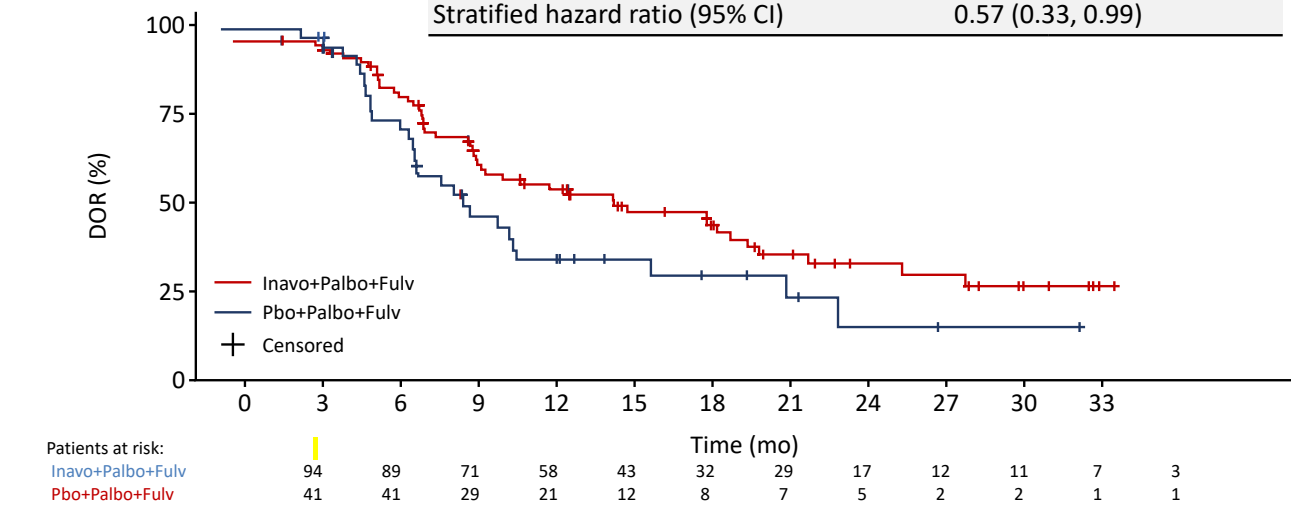
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Jhavery K, et al. SABCS 2023.

INAVO120: ORR and DOR



	Inavo+Palbo +Fulv (n=94)	Pbo+Palbo+Fulv (n=41)
No. of events, n (%)	46 (48.9)	27 (65.9)
Median (95% CI), mo	**18.4 (10.4, 22.2)**	**9.6 (7.4, 16.6)**
Stratified hazard ratio (95% CI)	0.57 (0.33, 0.99)	



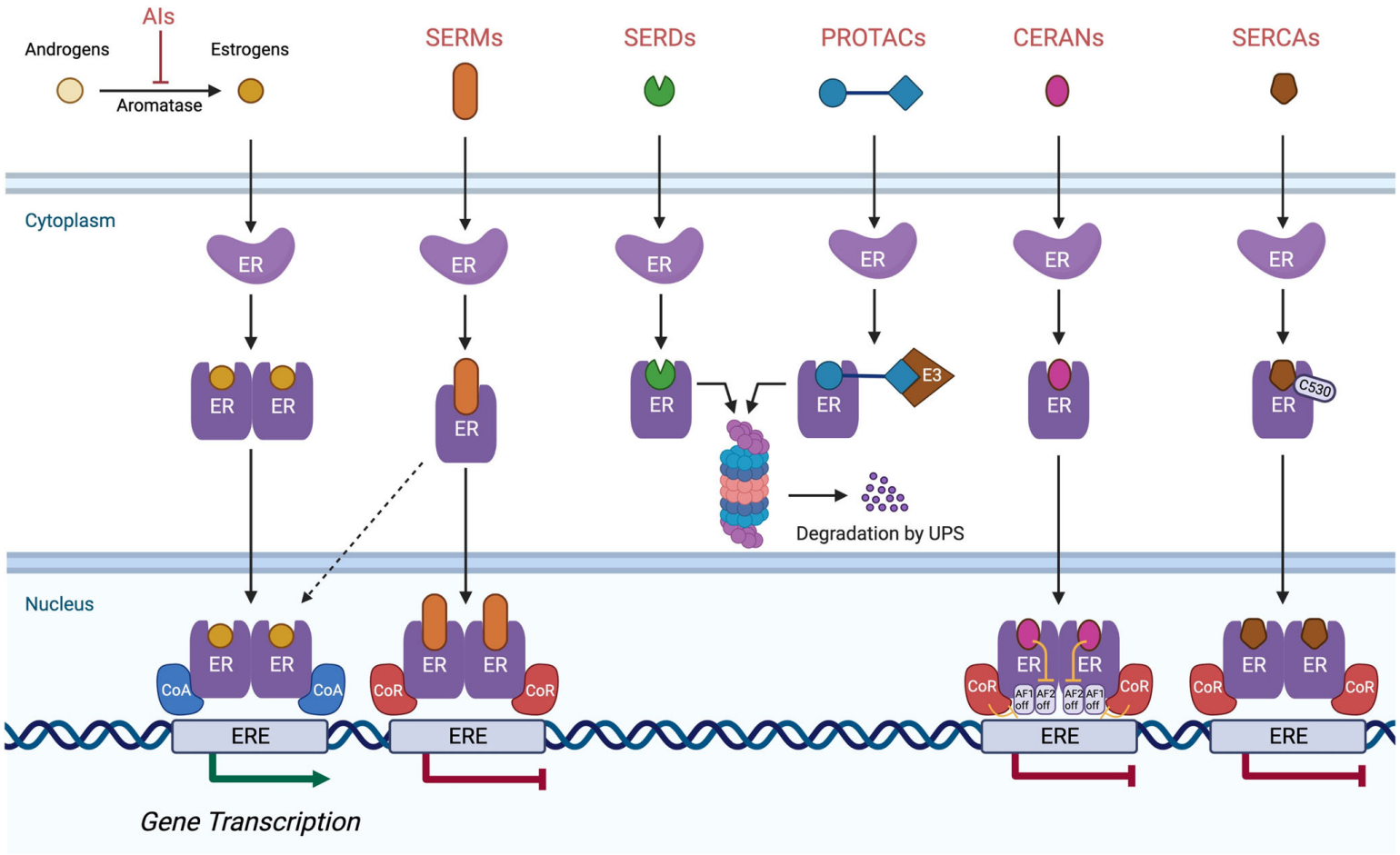
Jhavery K, et al. SABCS 2023.

REVIEW ARTICLE OPEN

Check for updates

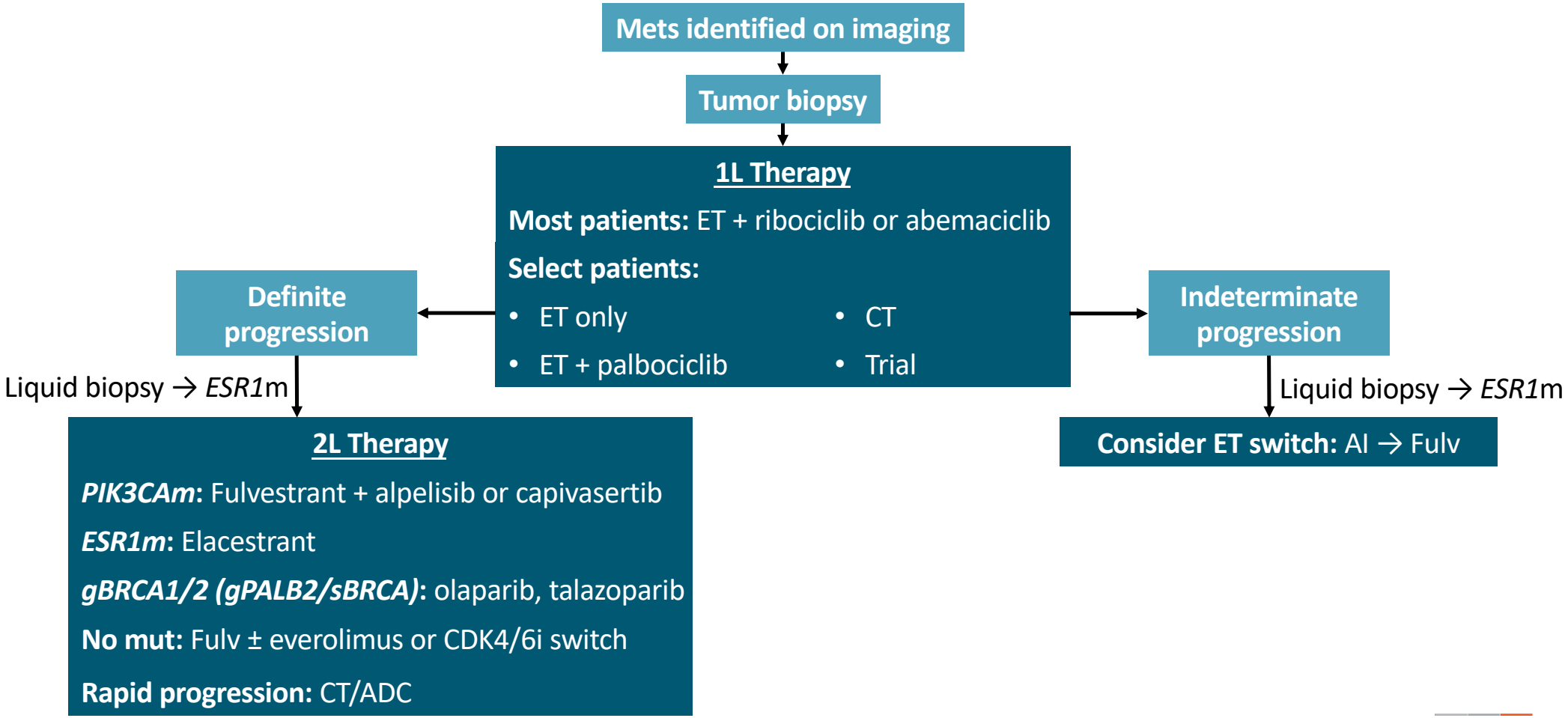
An emerging generation of endocrine therapies in breast cancer: a clinical perspective

Rima Patel[1]✉, Paula Klein[1], Amy Tiersten[1] and Joseph A. Sparano[1]



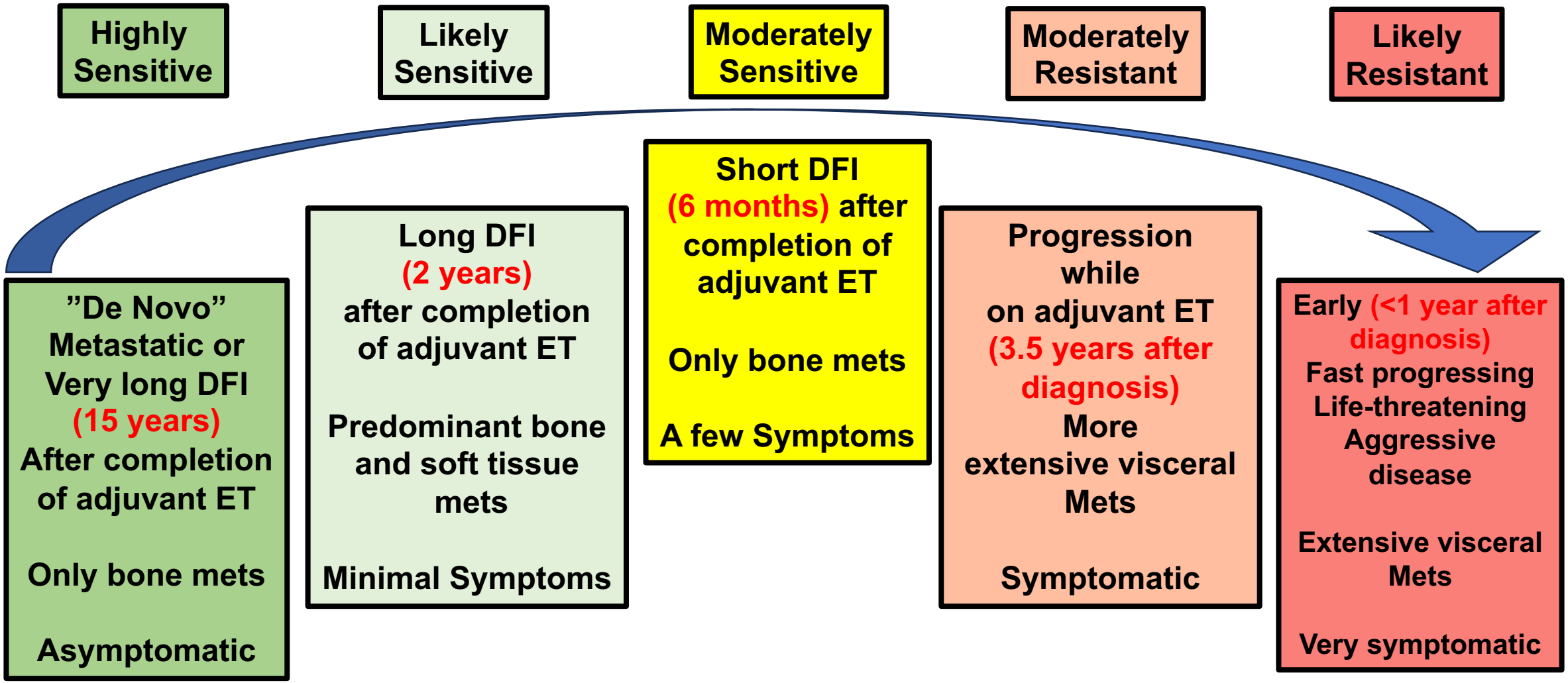
Patel R, et al. NPJ Breast Cancer 2023.

Current Approach to Newly Diagnosed HR+/HER2- MBC



Stover ASCO 2023.

Heterogeneity of HR+ Disease



Llombard-Cusac A, et al, 2022; Adapted from Barrios C, at SBCS 2013.

Summary

- Conceptually, ET has changed forever!
- Therapeutic decisions following a progression of ET and CKD 4/6i should be made on genomic analysis of tumor or ctDNA.
- Alpelisib or Capasertib for *PIK3CA*-mutated and elacestrant for *ERS1-mutated* cancer.
- If no actionable mutations switch CDK 4/6i or Everolimus + ET.
- The sequence may be impacted as ADCs move up in treatment plan.
- Our ability to identify different clinical and biological profiles within this patient population is the most important factor in improving therapies and outcomes.

Oncology Consultants
Overcoming Cancer.™

Thank you!

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