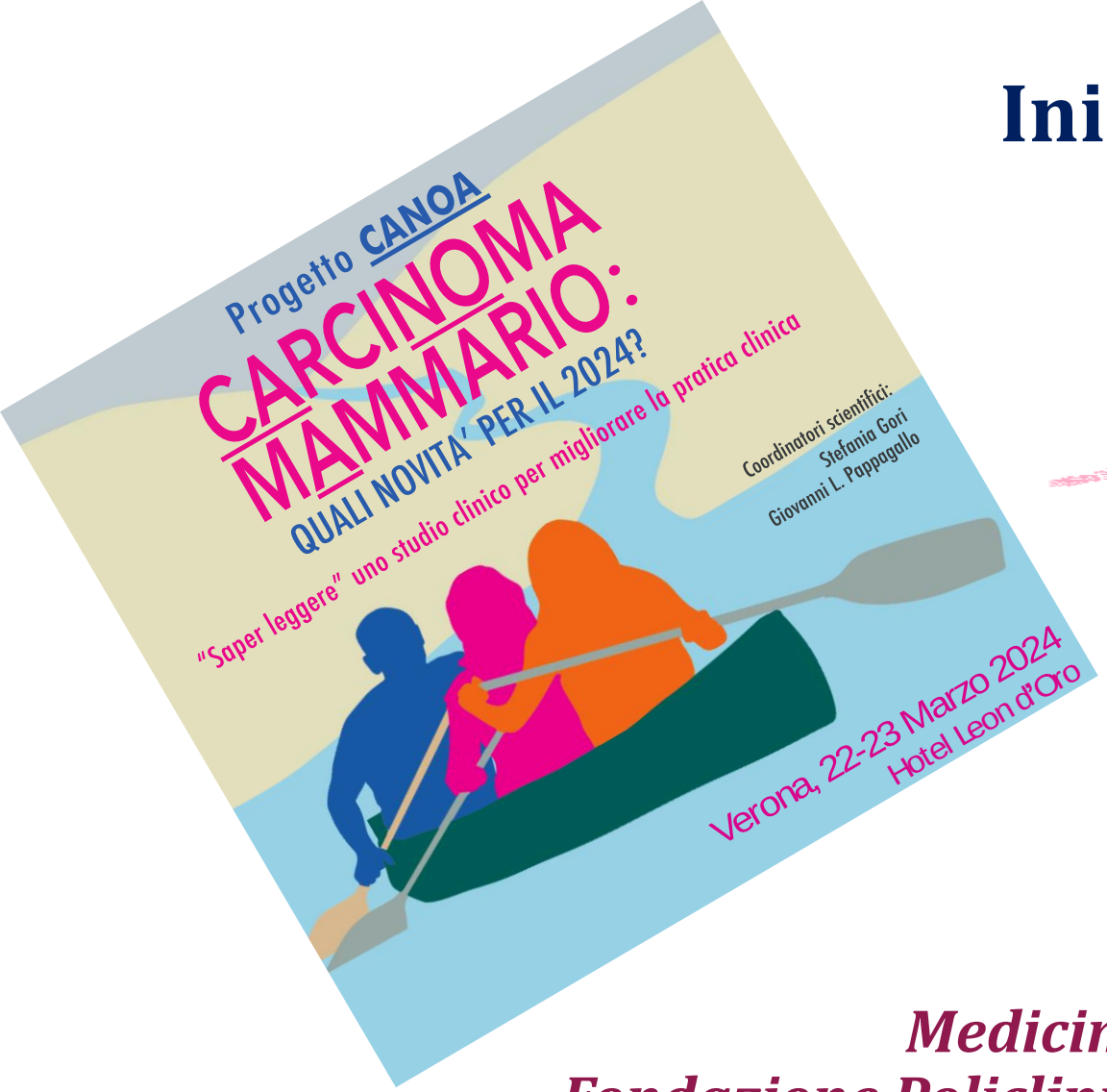

Inibitori di CDK 4/6 in Associazione a Ormonoterapia: Nuove Opzioni Terapeutiche Adiuvante

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Disclosures

Scientific Advisory Board, Meeting, Congress, Consulent:

Astra Zeneca

Dompè

Daiichi Sankyo Eisai

Exact Science

Gilead

Lilly

Menarini

Novartis

Pfizer

Roche

Seagen

Pierre Fabre

Thoughts from Clinical Practice Today in '*Canoa Day*'

Who benefits from CDK4/6 inhibitors?

May we believe to Predictive Factors?

Moving on....

Thoughts from Clinical Practice Today in '*Canoa Day*'

Who benefits from CDK4/6 inhibitors?

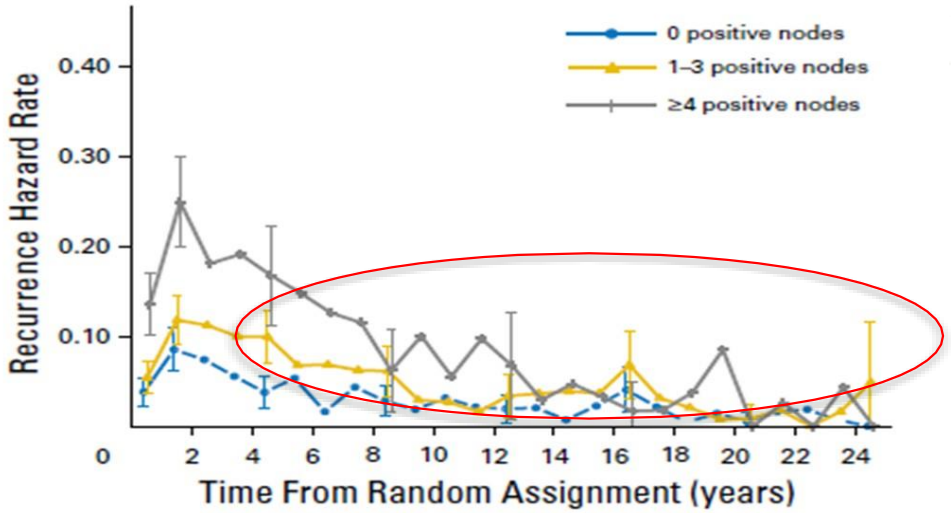
May we believe to Predictive Factors?

Moving on....

Rationale for Adjuvant CDK4/6 Inhibitors

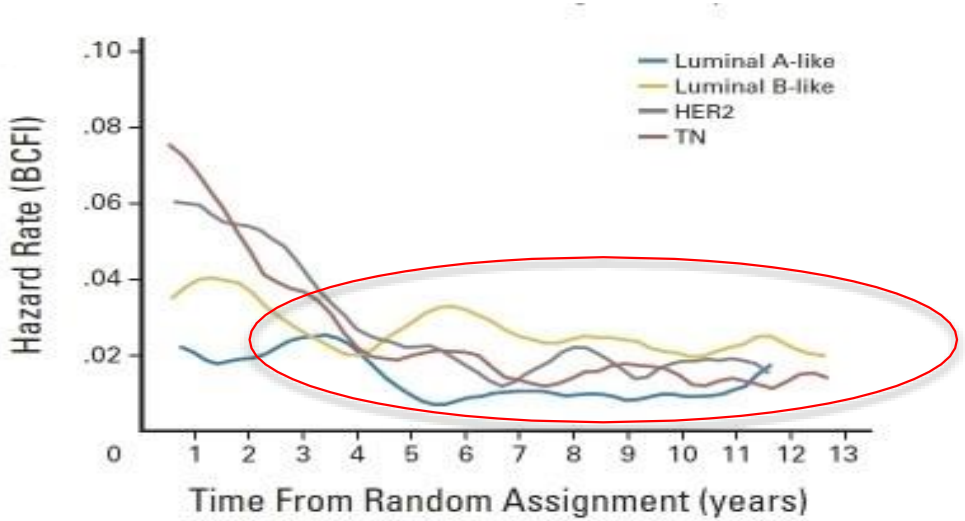
- ER+ breast cancer has a prolonged and persistent hazard of recurrence

IBCSG Trials I to V
Hazard of recurrence by nodal status



Colleoni et al, JCO 2016

IBCSG Trials I to V
Hazard of Recurrence by BC Subtypes



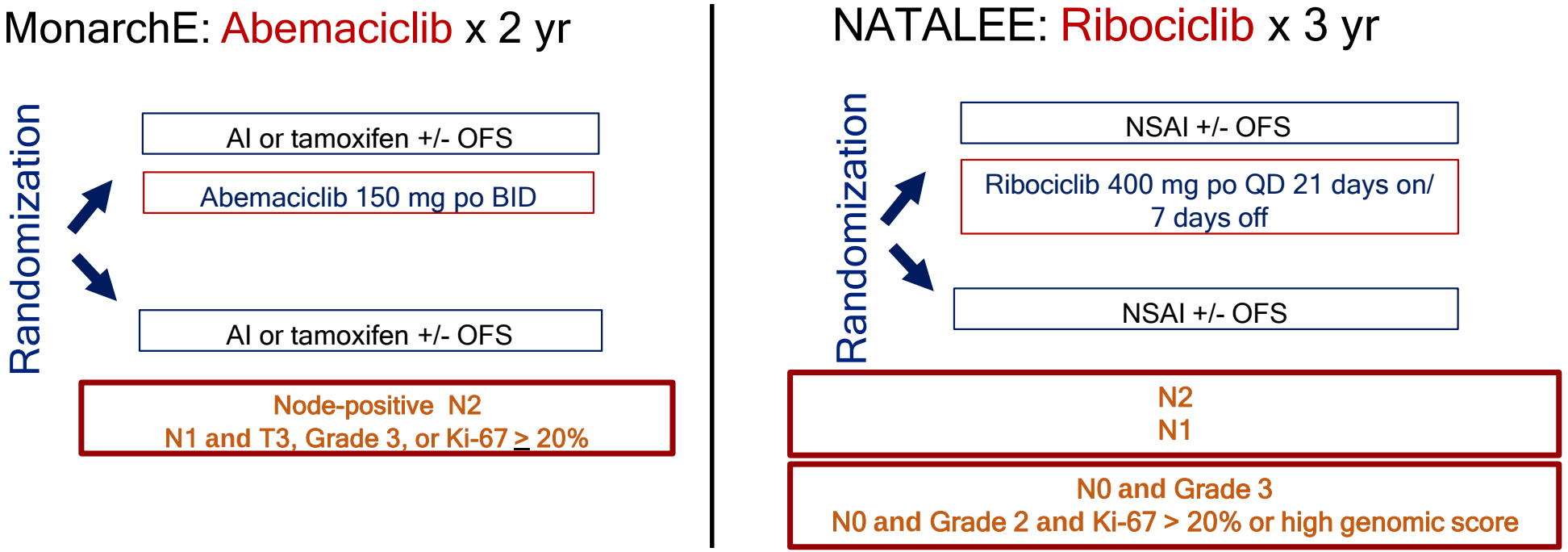
Metzger et al, JCO 2013

Studies Evaluating Adjuvant CDK4/6 inhibitors

	PALLAS (N=5760) Palbociclib	PENELOPE B (N=1250) Palbociclib	monarchE (N=5637) Abemaciclib	NATALEE (N=5101) Ribociclib
Population median age	Pre/postmen, men 52 yr	Pre/postmen 49 yr	Pre/postmeno, men 51 yr	Pre/postmeno, men
Stage IIA / IIB / III	18% / 33% / 49%	(No pCR after NACT; CPS-EG≥3; or 2 & ypN+)	12% / 14% / 74%	IIA, IIB, III (limited ~40% II)
Primary endpoint met	No	No	Yes	Yes

Mayer et al 2021; Loibl et al 2021, Johnston et al 2022, Slamon D et al ASCO 2023

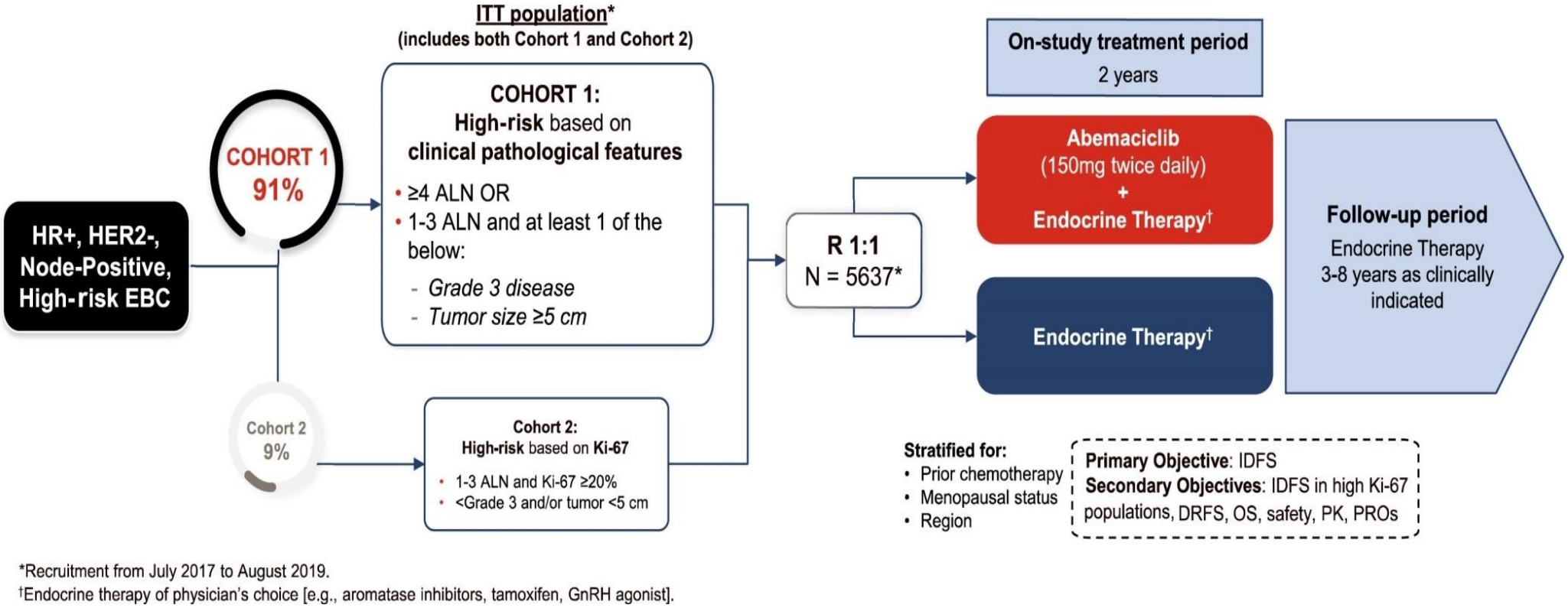
MonarchE and NATALEE Study Population



~30% pts early-stage tumors eligible for NATALEE and not MonarchE

Johnston S et al ESMO 2023; Slamon D et al ASCO 2023

monarchE Study Design (NCT03155997)

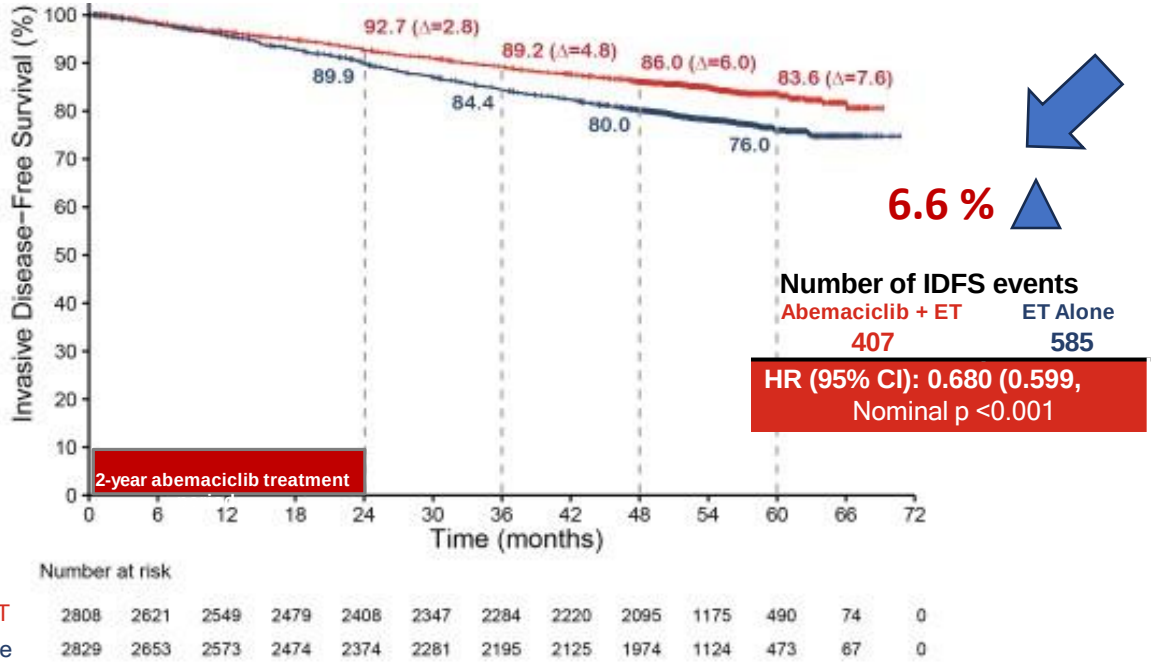


*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

Johnston et al, JCO2022, Harbeck et al. ESMO 2023

monarchE 5-yr Results

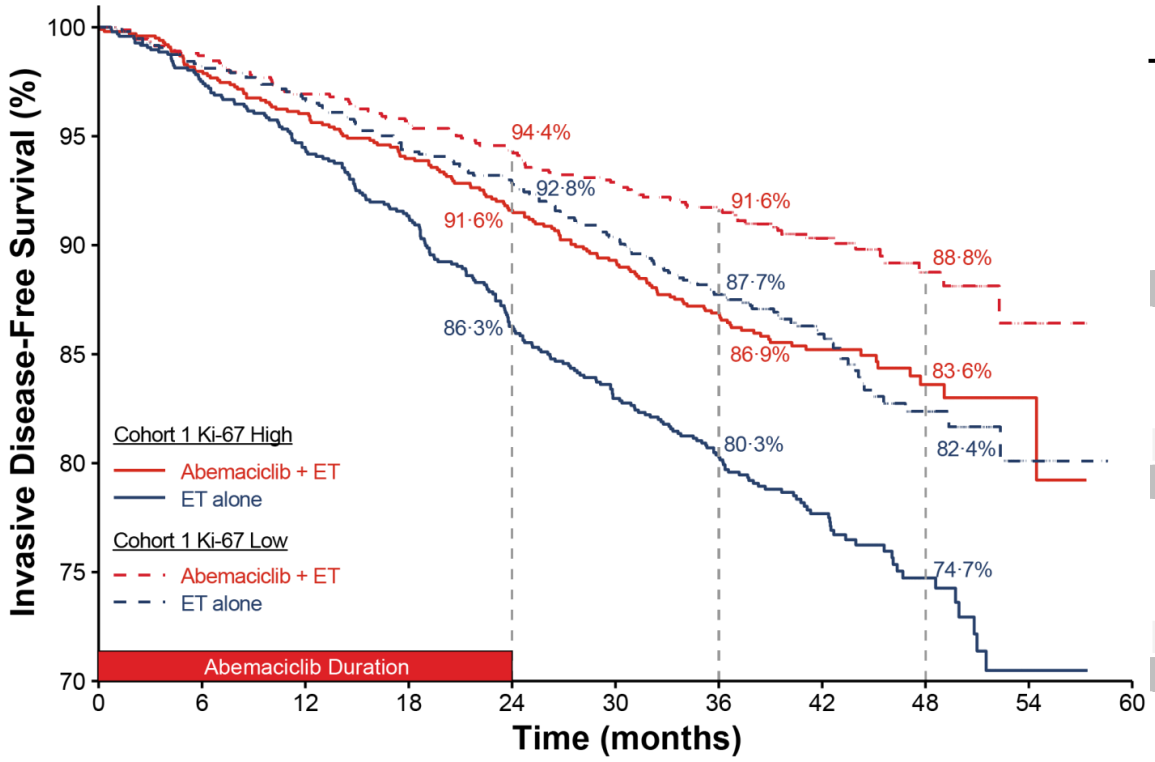
Median follow-up time is 4.5 years (54 months)



32% reduction in the risk of developing an IDFS event.

Harbeck et al. ESMO 2023

Ki-67 is Prognostic but Not Predictive of Abemaciclib Benefit

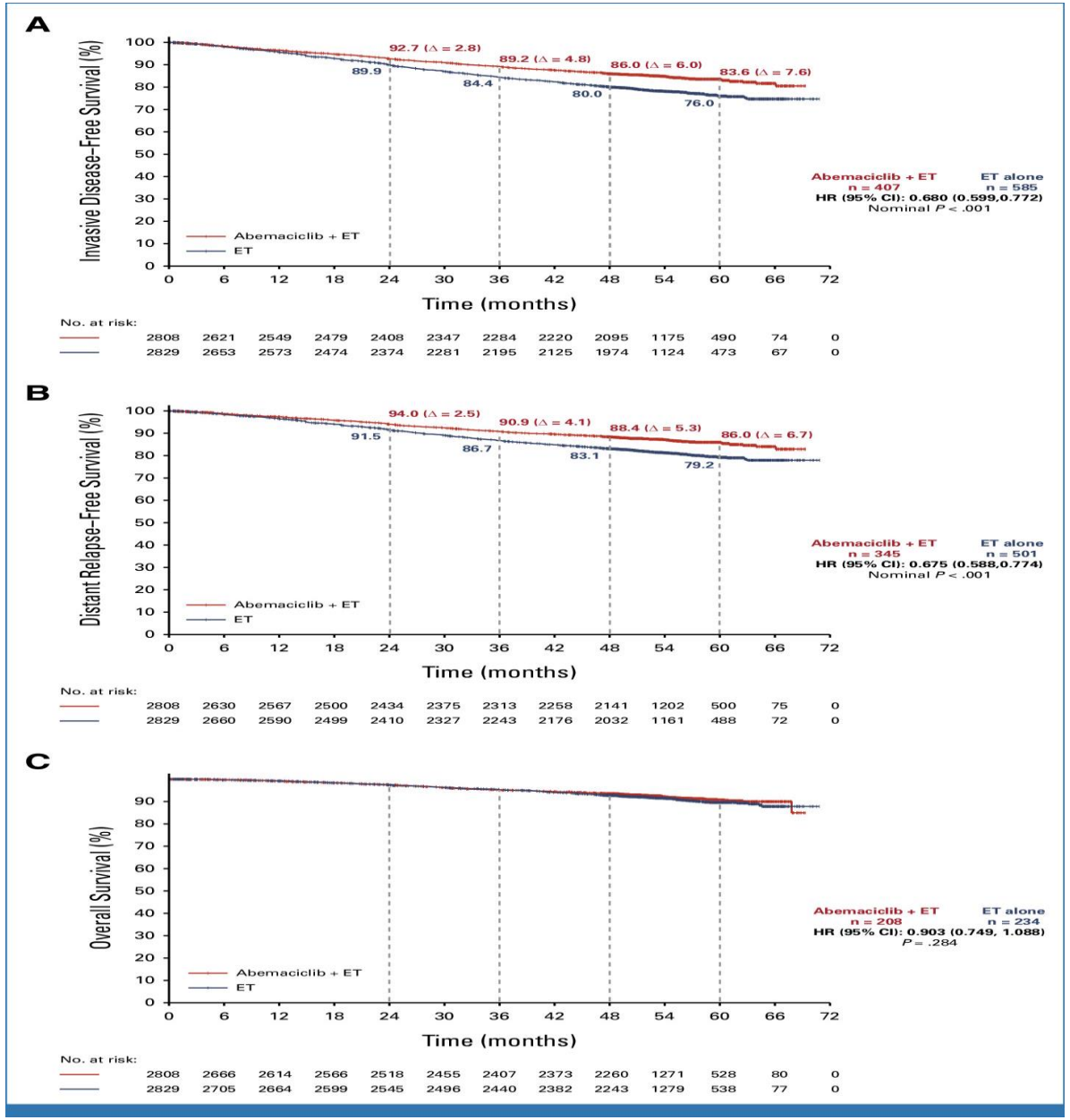


	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=10 17	ET alone N=98 6	Abemaciclib + ET N=94 6	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

*Ki-67 value was missing in 1203 (23.5%) patients

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

Johnston et al, JCO2022



Kaplan-Meier survival curves of (A) IDFS, (B) DRFS, and (C) OS in the intent-to-treat population.

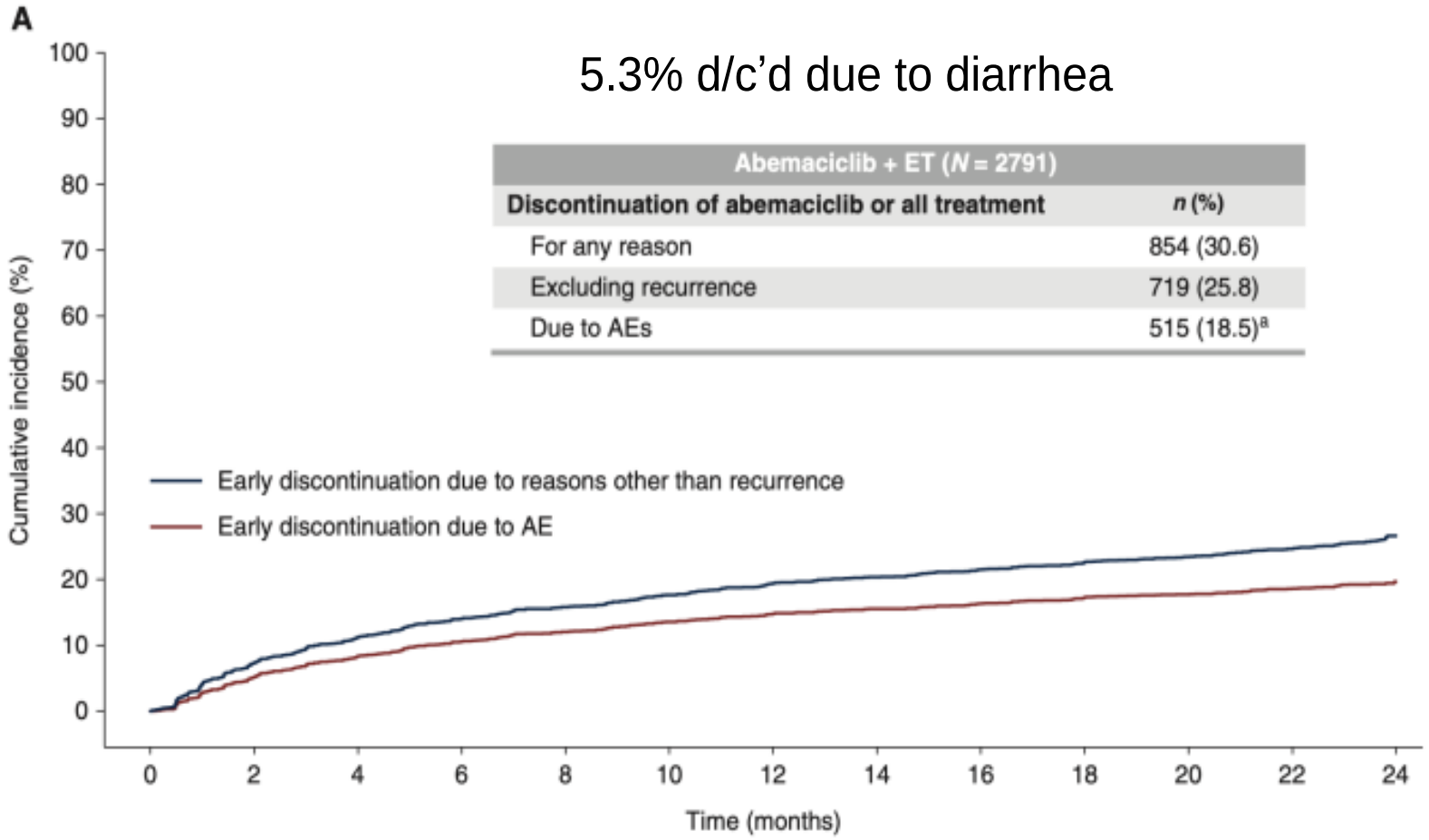
The addition of abemaciclib continued to be associated with improved IDFS, and DRFS over longer follow-up

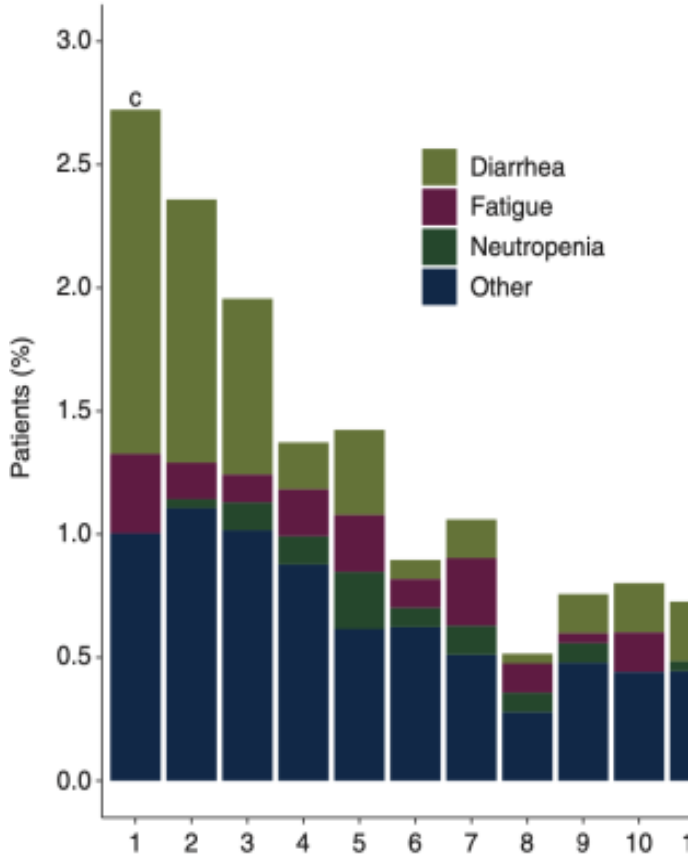
Rastogi et al J Clin Oncol 2024

monarchE: Abemaciclib Discontinuation Rate

5.3% d/c'd due to diarrhea

Abemaciclib + ET (*N* = 2791)	
Discontinuation of abemaciclib or all treatment	***n* (%)**
For any reason	854 (30.6)
Excluding recurrence	719 (25.8)
Due to AEs	515 (18.5)[a]

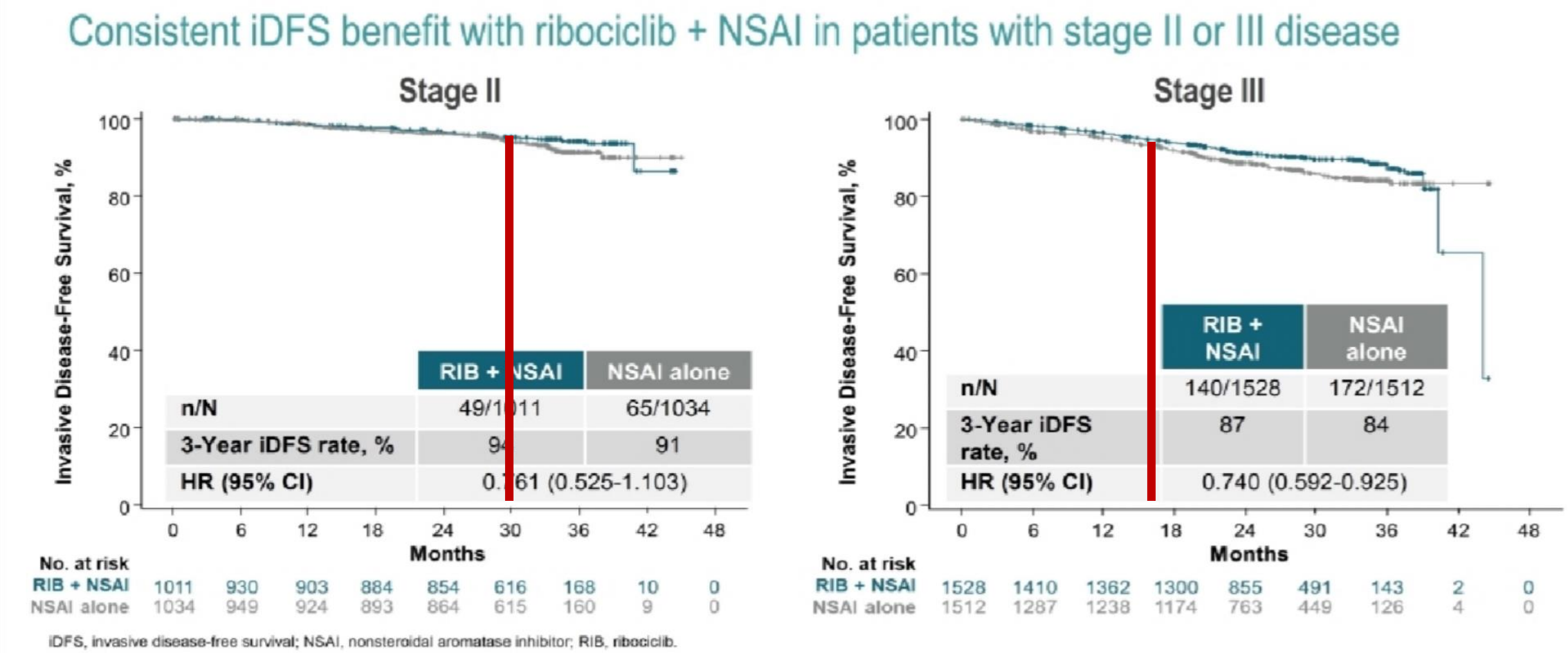




Highest rates of d/c of tx were early

Rugo HS et al Ann Oncology 2022

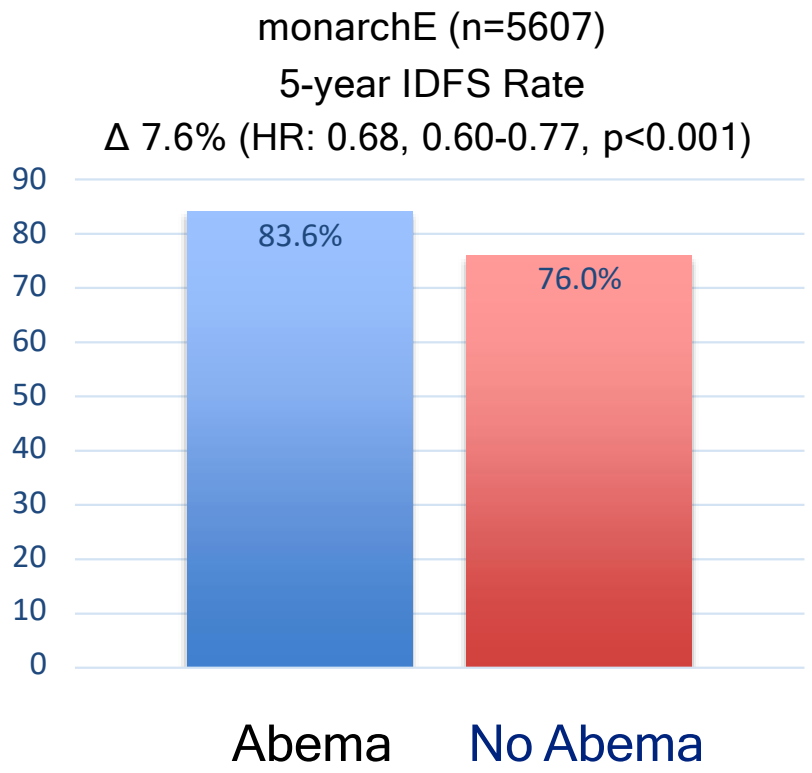
NATALEE iDFS by anatomic stage



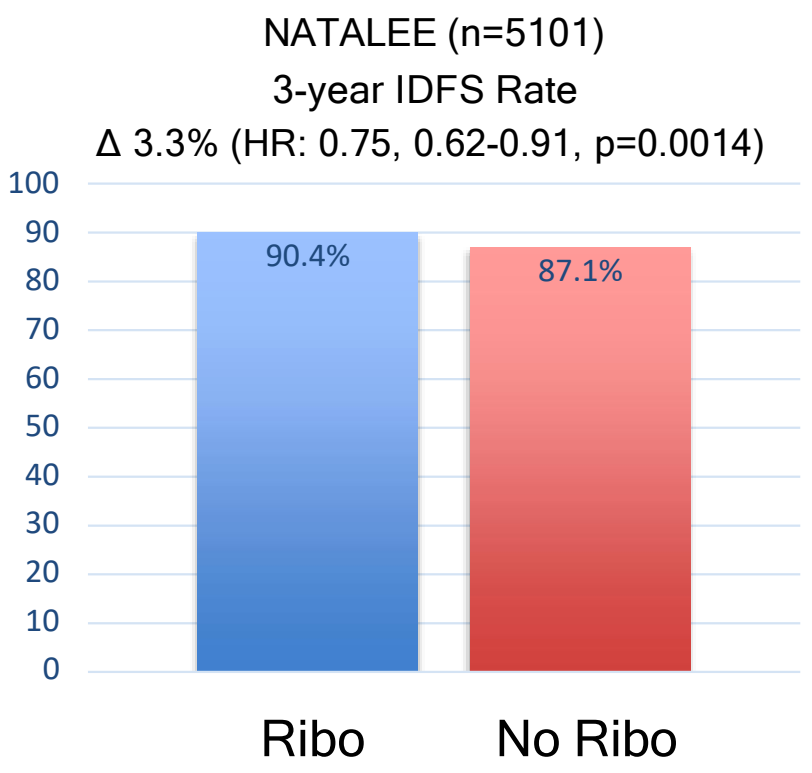
iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Slamon et al NEJM 21 March 2024

monarchE and NATALEE: IDFS Rate



Distant Relapse Free Survival 5-year rate: Δ 6.7%

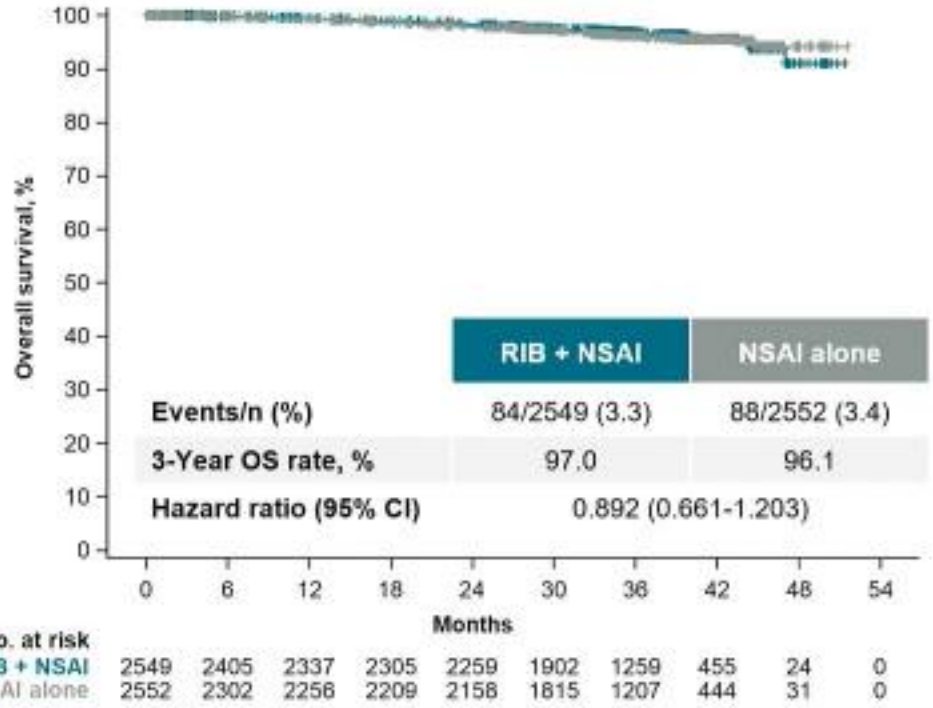


Distant Disease Free Survival 3-year rate: Δ 2.2%

Johnston S et al Lancet Oncology 2023; Johnston S et al ESMO 2023; Slamon D et al ASCO 2023

NATALEE OS

Overall Survival



	RIB + NSAI	NSAI alone
Events/n (%)	84/2549 (3.3)	88/2552 (3.4)
3-Year OS rate, %	97.0	96.1
Hazard ratio (95% CI)	0.892 (0.661-1.203)	

- The median follow-up for OS was 35.9 months at the final analysis
- The OS data require longer-term follow-up, as there were fewer than 4% of events in both treatment arms

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Hortobagy et al 2024 SABCS 2013

Slamon et al NEJM 21 March 2024

What have we learned from MonarchE and NATALEE?

- Consistent treatment benefits with CDK4/6 inhibitors across patient subsets
- MonarchE: substantial and persistent benefit with adjuvant abemaciclib
- Natalee: encouraging results with adjuvant ribociclib, but notable differences in the absolute benefit for stage II vs. III

Long-term follow-up will be essential to understanding the magnitude of treatment benefits and survival outcomes

Will we be able to identify a predictive biomarker?

Or will we see a similar story when compared to adjuvant hormonal therapy?

Thoughts from Clinical Practice Today in '*Canoa Day*'

Who benefits from CDK4/6 inhibitors?

May we believe to Predictive Factors?

Moving on....

	Primary endocrine resistant cohort (n = 72)	Secondary endocrine resistant cohort (n = 207)	Endocrine sensitive cohort (n = 214)	p
Median age at metastasis, years (range)	61 (33–81)	62 (39–87)	65 (34–89)	0.008
Age				0.053
≤50	8 (11.1%)	25 (12.1%)	22 (10.3%)	
51–64	35 (48.6%)	95 (45.9%)	74 (34.6%)	
≥65	29 (40.3%)	87 (42.0%)	118 (55.1%)	
Menopausal status				0.106
Premenopausal	6 (8.3%)	31 (15.0%)	40 (18.7%)	
Postmenopausal	66 (91.7%)	176 (85.0%)	174 (81.3%)	
Type of surgery				0.087
Breast conserving surgery	35 (48.6%)	128 (61.8%)	115 (53.7%)	
Mastectomy	37 (51.4%)	79 (38.2%)	99 (46.3%)	
Histologic type				0.790
Ductal	50 (69.4%)	158 (76.3%)	162 (75.7%)	
Lobular	18 (25.0%)	38 (18.4%)	40 (18.7%)	
Other	4 (5.6%)	11 (5.3%)	12 (5.6%)	
Tumor size (T)				0.361
pT1	26 (36.1%)	93 (44.9%)	97 (45.3%)	
pT2/3/4	46 (63.9%)	114 (55.1%)	117 (54.7%)	
Nodal status (N)				0.042
N0	11 (15.3%)	37 (17.9%)	43 (20.1%)	
N1	18 (25.0%)	83 (40.1%)	87 (40.7%)	
N2/3	43 (59.7%)	87 (42.0%)	84 (39.3%)	
Tumor grading (G)				0.011
G1	4 (5.6%)	8 (3.9%)	11 (5.1%)	
G2	28 (38.9%)	126 (60.9%)	131 (61.2%)	
G3	40 (55.6%)	73 (35.3%)	72 (33.6%)	
Hormone receptor status				0.146
ER+/PgR+	67 (93.1%)	193 (93.2%)	197 (92.1%)	
ER+/PgR–	5 (6.9%)	14 (6.8%)	12 (5.6%)	
ER–/PgR+	0 (0.0%)	0 (0.0%)	5 (2.3%)	
Treatment received				0.149
Standard	46 (63.9%)	105 (50.7%)	113 (52.8%)	
Experimental	26 (36.1%)	102 (49.3%)	101 (47.2%)	
Average BMI (range)	27.8 (19.5–48.5)	26.6 (16.9–45.3)	25.7 (14.8–41.5)	0.006
BMI				0.055
<25	23 (31.9%)	74 (35.8%)	93 (43.5%)	
25–29.9	21 (29.2%)	78 (37.7%)	73 (34.1%)	
≥30	28 (38.9%)	55 (26.6%)	48 (22.4%)	
Previous (neo) adjuvant chemotherapy and type				0.002
No chemotherapy	15 (20.8%)	34 (16.4%)	28 (13.1%)	
Anthracycline-based	10 (13.9%)	58 (28.0%)	87 (40.7%)	
Anthracycline- and taxane-based	45 (62.5%)	105 (50.7%)	92 (43.0%)	
Taxane-based	2 (2.8%)	8 (3.9%)	3 (1.4%)	
Other	0 (0.0%)	2 (1.0%)	4 (1.9%)	
Adjuvant endocrine therapy				NA
None	0 (0.0%)	0 (0.0%)	27 (12.6%)	
Tamoxifen only	14 (19.4%)	41 (19.8%)	37 (17.3%)	
Aromatase inhibitors	25 (34.7%)	57 (27.5%)	18 (8.4%)	
Tamoxifen → aromatase inhibitors	33 (45.8%)	109 (52.6%)	132 (61.7%)	
Duration of endocrine therapy (months, range)	15.1 (0.1–24.0)	42.9 (2.0–97.6)	60.4 (0.0–100.5)	NA
Type of metastatic presentation				0.005
Non visceral	26 (36.1%)	99 (47.8%)	123 (57.5%)	
Visceral	46 (63.9%)	108 (52.2%)	91 (42.5%)	

(Table 1 continues on next page)

Prognostic and clinical impact of the endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer: an individual patient-level analysis from the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) studies

Matteo Lambertini,[a,b,x,*] Eva Blondeaux,[c,x] Giancarlo Bisagni,[d] Silvia Mura,[e] Sabino De Placido,[f] Michelino De Laurentiis,[g] Alessandra Fabi,[h] Anita Rimanti,[i] Andrea Michelotti,[j] Mauro Mansutti,[k] Antonio Russo,[l] Filippo Montemurro,[m] Antonio Frassoldati,[n] Antonio Durando,[o] Stefania Gori,[p] Anna Turletti,[q] Stefano Tamberi,[r] Ylenia Urracci,[s] Piero Fregatti,[t,u] Maria Grazia Razeti,[a,b] Roberta Caputo,[g] Carmine De Angelis,[f] Valeria Sanna,[e] Elisa Gasparini,[d] Elisa Agostinetto,[v] Evandro de Azambuja,[v] Francesca Poggio,[w] Luca Boni,[c] and Lucia Del Mastro[a,b]

EClinicalMedicine 2023

MIG1 – GIM2-GIM3-GIM4

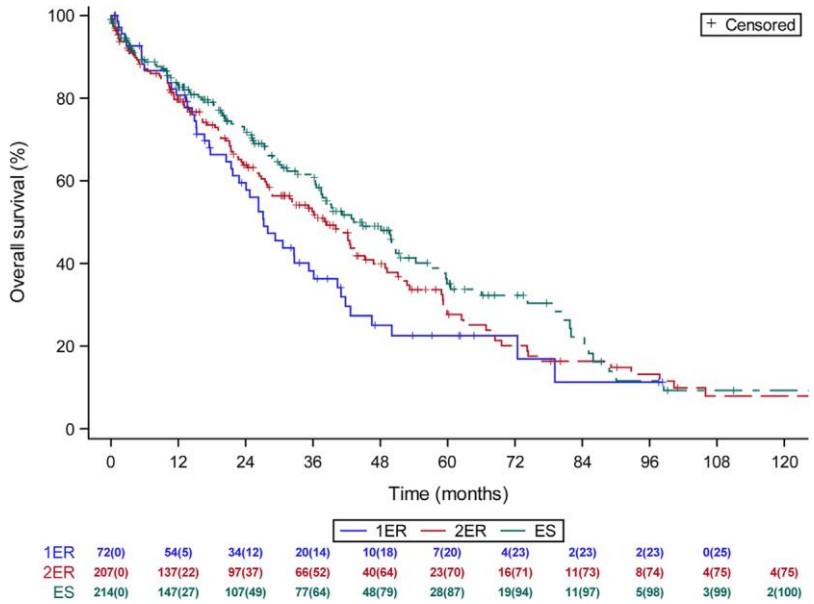


Fig. 3: **Overall survival computed from the date of distant relapse and death from any cause between endocrine sensitive, primary or secondary endocrine resistant cohorts.** 1ER, primary endocrine resistant; 2ER, secondary endocrine resistant; ES, endocrine sensitive.

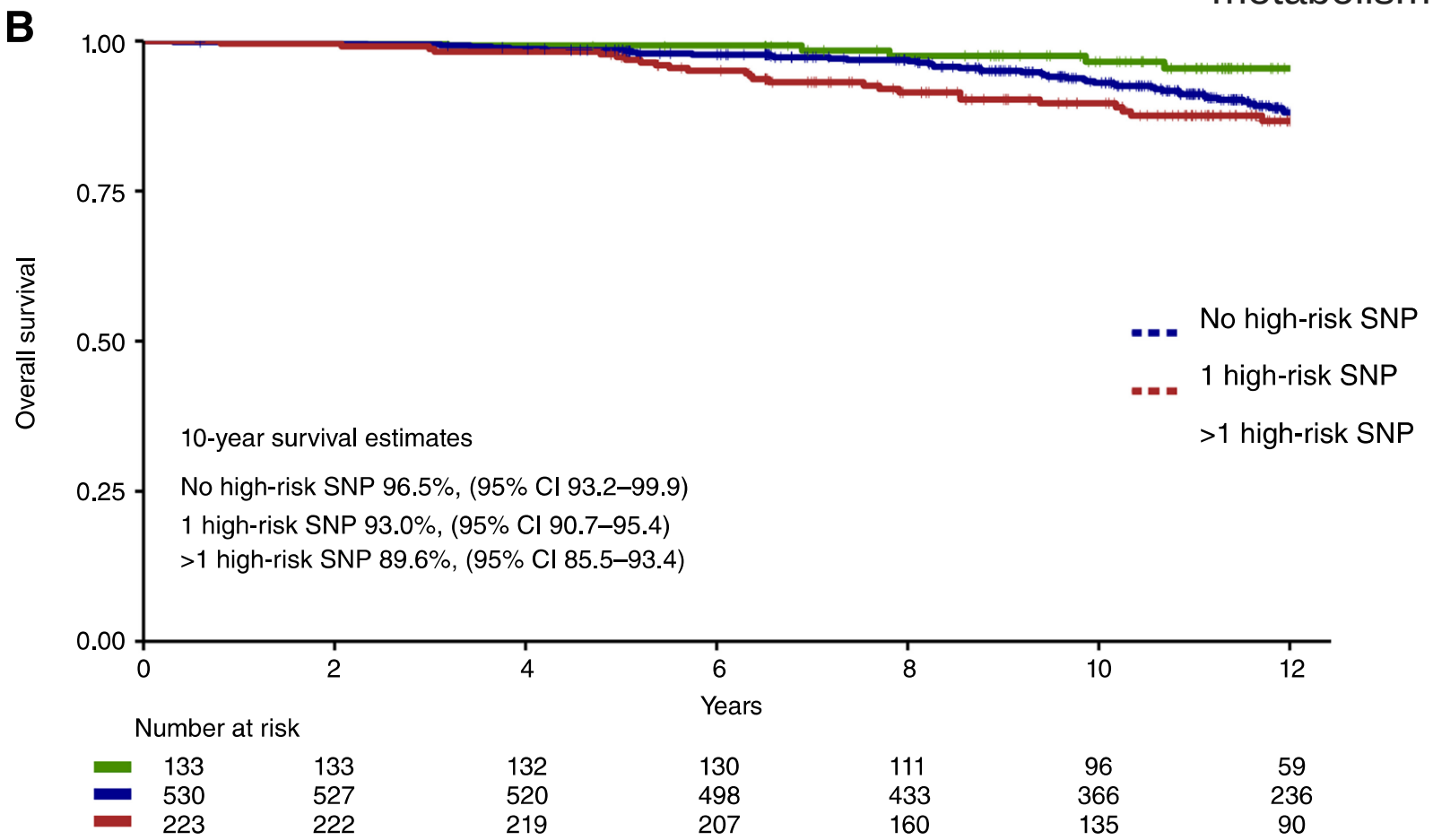
Patients with primary endocrine resistance were relatively younger, had more often node positive disease and grade 3 tumour, and developed more frequently visceral relapses and specifically liver metastases

Primary endocrine resistance was associated with the worst prognosis

The distinctive time-dependent and site- specific recurrence patterns needs to be considered in the survivorship trajectory of these patients. Considering its prognostic and clinical impact, the currently adopted endocrine resistance/sensitivity classification may be considered a valid tool to guide clinical decision-making and to design future endocrine therapy trials in the metastatic setting

SNP of Aromatase Predict Long-term Survival and Aromatase Inhibitor Toxicity in Patients with Early Breast Cancer: A Biomarker Analysis of the GIM4 and GIM5 Trials

single-nucleotide polymorphisms (SNP) in the aromatase gene might affect aromatase inhibitors metabolism and efficacy



Conte et al, Clin Cancer Res 2023

Definition of High-Risk Early Hormone-Positive HER2—Negative Breast Cancer: A Consensus Review

Mattia Garutti [1,*,†], Gaia Griguolo [2,3,†], Andrea Botticelli [4], Giulia Buzzatti [5], Carmine De Angelis [6], Lorenzo Gerratana [1], Chiara Molinelli [5], Vincenzo Adamo [7], Giampaolo Bianchini [8,9], Laura Biganzoli [10], Giuseppe Curigliano [11,12], Michelino De Laurentiis [13], Alessandra Fabi [14], Antonio Frassoldati [15], Alessandra Gennari [16,17], Caterina Marchiò [18,19], Francesco Perrone [20], Giuseppe Viale [12,21], Claudio Zamagni [22], Alberto Zambelli [23], Lucia Del Mastro [5,24,‡], Sabino De Placido [6,‡], Valentina Guarneri [2,3,‡], Paolo Marchetti [25,‡] and Fabio Puglisi [1,26,‡]

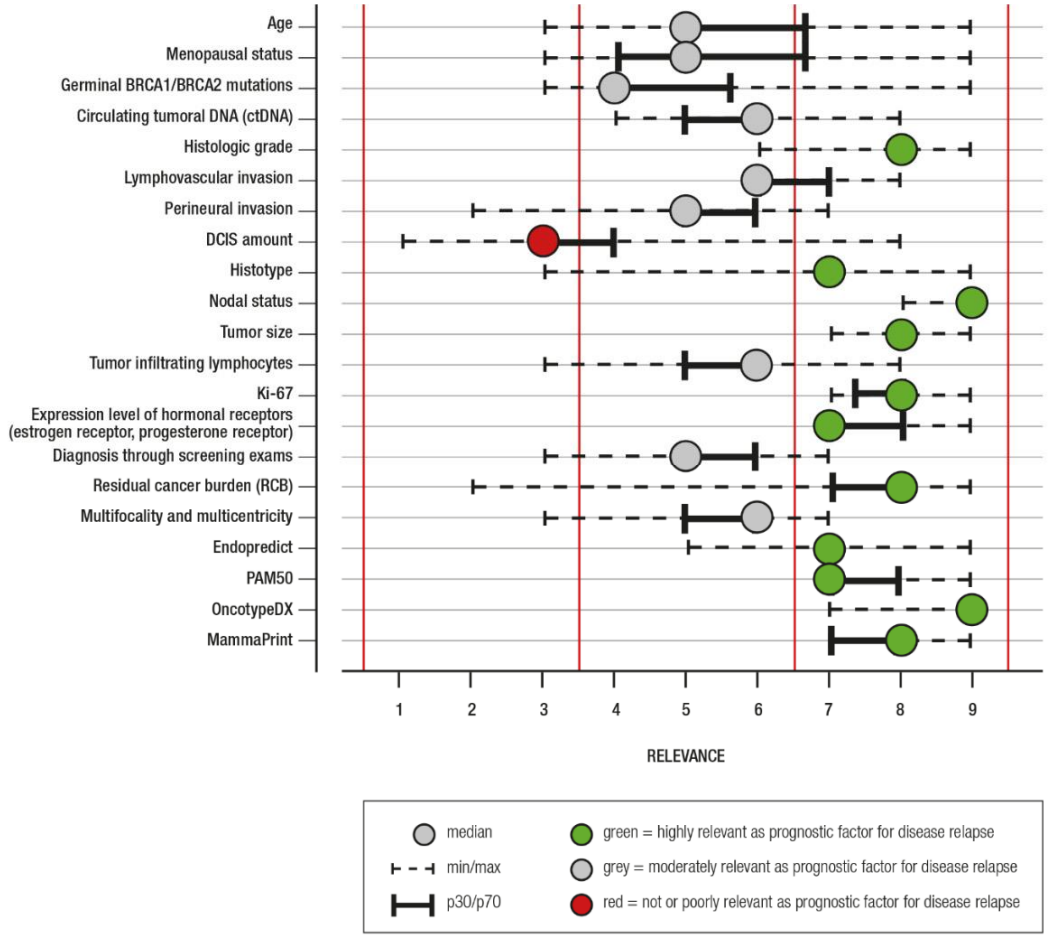
The IRIDE (hIGh Risk DEfinition in breast cancer) working group

A RAND consensus method was used to define the relevance of each risk factor. Among the 21 features included, 12 were considered relevant risk factors for relapse.

Table 1. Preliminary list of prognostic factors prognostic of for disease relapse.

Clinical, Pathological, and Morphological Factors
• Age
• Menopausal status
• Germinal *BRCA1/BRCA2* mutations
• Circulating tumoral DNA
• Histological grade
• Lymphovascular invasion
• Perineural invasion
• DCIS amount
• Histotype
• Nodal status (N)
• Tumor size (T)
• Tumor-infiltrating lymphocytes
• Ki-67
• Expression level of hormonal receptors (ER, PgR)
• Diagnosis through screening exams
• Residual cancer burden
• Multifocality and multicentricity
Genomic Factors
• EndoPredict®
• PAM50
• Oncotype DX
• MammaPrint®

DCIS: ductal carcinoma in situ, ER: estrogen receptor, PgR: progesterone receptor.



Cancers 2022

ANAMNESI
59 anni
Menopausa

COMORBIDITA'
Diabete mellito di tipo II
Trattamento: Metformina 500 mg x 2/die

Concepts and Thoughts

STADIAZIONE TNM E BIOLOGIA DELLA MALATTIA
pT2m 2.1 cm N1 2/18, **G3, ER 95%, PgR 75%, Ki67 25%, HER2 0**

INTERVENTO CHIRURGICO
Mastectomia sinistra skin sparing + BLS + linfadenectomia ascellare.
Carcinoma duttale invasivo pT2m (2.1 cm) N1 2/14, G3, ER 95%, PgR 75%, Ki67 25%, HER2 0)

11/2023 → **12/2023**

PRESENTAZIONE E DECORSO CLINICO
Ecografia + Rx mammografia di screening: 3 noduli (diam 2.5, 1.5, 1.2 cm) nei QQEE della mammella sinistra.

Esame istologico su biopsia del nodulo di maggiore dimensione QSE sinistra: **carcinoma duttale invasivo** (**cT2m** 2.5 cm **cN0 G3, ER 95%, PgR 75%, Ki67 20%, HER2 0**).

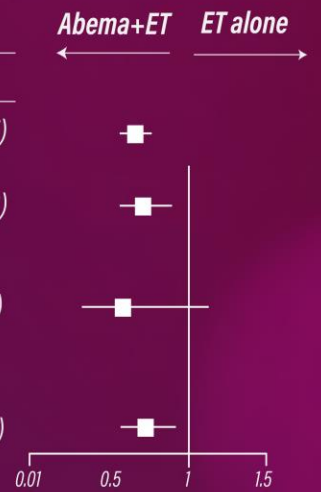
STADIAZIONE
TAC e scintigrafia ossea: non lesioni secondarie
Oncotype DX: RS 18

Inferred 21-gene Oncotype risk scores (MonarchE trial)

Observed high percentage of tumors with >25 risk score, reflective of the high-risk patient population

TREATMENT BENEFIT OBSERVED IN INFERRED ONCOTYPE RISK SCORES (MonarchE TRIAL)

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4yr IDFS Rate (95% CI)	Events/n (%)	4yr IDFS Rate (95% CI)	HR (95% CI)
ITT	407/2808 (14%)	86.0 (84.7-87.3)	585/2829 (21%)	80.0 (78.5-81.6)	0.68 (0.60, 0.77)
Biomarker Subset	138/605 (23%)	77.4 (74.1-80.9)	182/585 (31%)	69.8 (66.1-73.7)	0.70 (0.56, 0.88)
Inferred Oncotype-RNA score <=25	18/173 (10%)	90.2 (85.8-94.9)	28/165 (17%)	84.2 (78.7-90.1)	0.59 (0.33, 1.10)
Inferred Oncotype-RNA score>25	120/432 (28%)	72.3 (68.1-76.8)	154/420 (37%)	64.1 (59.6-69)	0.73 (0.57, 0.92)



Interaction p-value (inferred Oncotype scores high and low) = 0.532

- **The selected biomarker subset is enriched for IDFS events using case-cohort design**
- **IDFS rates are presented as indicative of relative prognosis across subtypes but do not inform the actual risk of recurrence within each subtype because of IDFS enrichment**

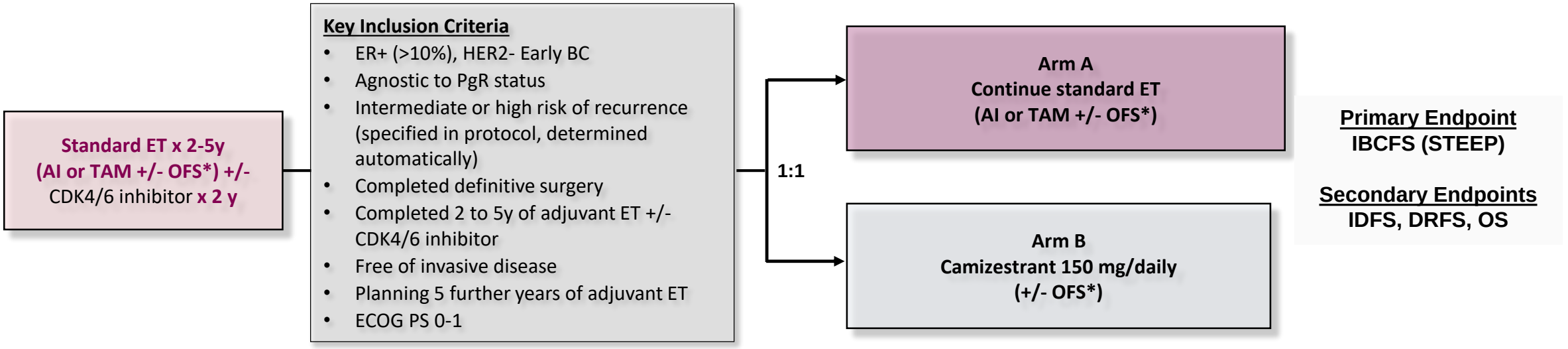
Thoughts from Clinical Practice Today in '*Canoa Day*'

Who benefits from CDK4/6 inhibitors?

May we believe to Predictive Factors?

Moving on....

CAMBRIA-1 Study Design



* Pre-menopausal women and men will receive ovarian function suppression (OFS) mandatory in Camizestrant arm, per local guideline in control arm

The study also requires at least 430 patients to have received a prior adjuvant CDK4/6 inhibitor. In addition, 645 patients will be recruited from China.

Stratification Factors

• Risk	High[a]	Intermediate[b]
• Duration of prior adjuvant ET	24 to <42 mo	≥ 42 to 63 mo
• Menopausal status	Pre, Peri, Men	Post
• Prior ET	Tamoxifen	AI
• Prior adjuvant CDK4/6i	Yes	No

[a]**High-Risk** = T4, T3 N+, ≥ 4+ LN, T1c-T2, 1 LN+ with G3 or Ki67 >= 20%, or high-risk gen sig, T1a-T2, 2-3 LN+ with G3 or Ki67 >=20% or high-risk gen sig

[b]**Intermediate-Risk** = T3N0, T1c-T2 N0 with G3 or Ki67 >= 20%, or high-risk gen sig or prior chemotherapy, T1a-T2, 2-3 LN+ without G3, Ki67 >=20%, or high-risk gen sig

Based on Clinical Study Protocol v2.0 dated 14-Dec-2022

CAMBRIA-2

phase III, open-label, randomised study to assess the efficacy and safety of camizestrant (AZD9833, a next generation, oral selective estrogen receptor degrader) vs standard endocrine therapy (aromatase inhibitor or tamoxifen) as adjuvant treatment for patients with ER+/HER2- early breast cancer and an intermediate-high or high risk of recurrence who have completed definitive locoregional treatment and have no evidence of disease

Camizestrant (+/- Abemaciclib)

AI/TAM

WIDER STUDY

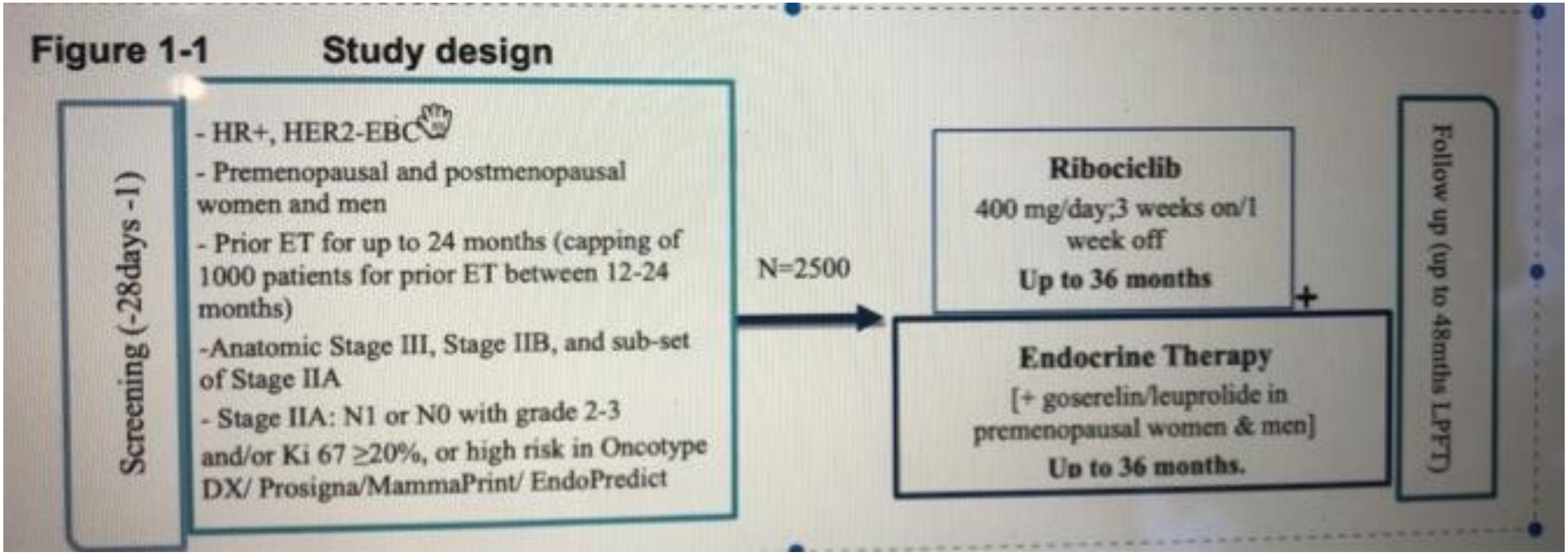


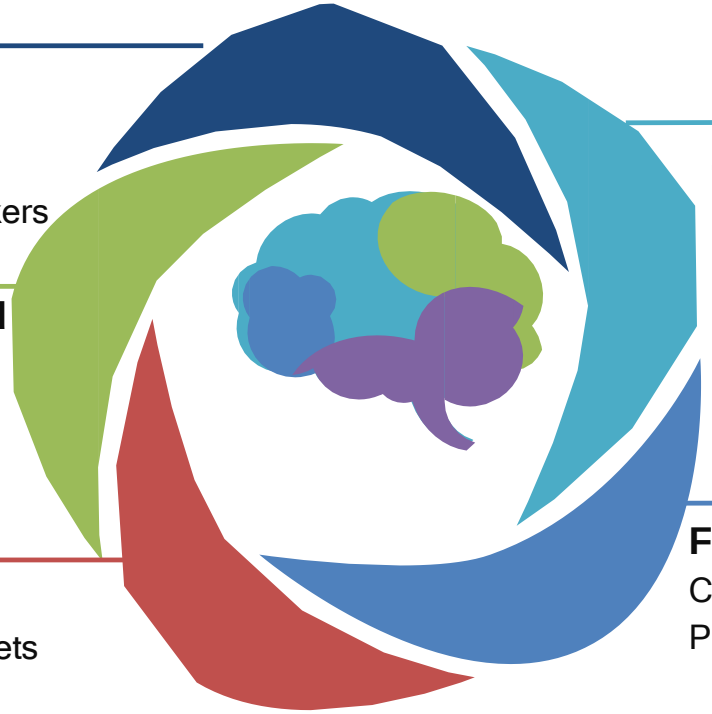
Figure 1-1 Study design
Screening (-28days -1)
- HR+, HER2-EBC
- Premenopausal and postmenopausal women and men
- Prior ET for up to 24 months (capping of 1000 patients for prior ET between 12-24 months)
-Anatomic Stage III, Stage IIB, and sub-set of Stage IIA
- Stage IIA: N1 or N0 with grade 2-3 and/or Ki 67 ≥20%, or high risk in Oncotype DX/ Prosigna/MammaPrint/ EndoPredict
N=2500
Ribociclib
400 mg/day;3 weeks on/1 week off
Up to 36 months
+
Endocrine Therapy
[+ goserelin/leuprolide in premenopausal women & men]
Up to 36 months.
Follow up (up to 48mths LPFU)

Risk Factors in early Dicision & the «NEW» Concept of Clinical Risk Factors

Risk stratification
- Genomic tools
  - Prognostic
  - Need for predictive biomarkers

When chemo is considered
- DD AC-T for high-risk
- Less intense regimens

CDK4/6 inhibitors
- Benefit consistent across subsets
- Risk stratification will be key



Thoughtful judgment
- Clinical decisions
- Data generation
- Patient preferences

Factors influencing risk

Comorbidities (e.g., obesity)

Physical exercise

Thank you for your attention