XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

Inhibidores de CDK 4/6
Papel en la adyuvancia

Fernando Moreno
Hospital Clínico San Carlos

Outline

- Natural history of ER+ HER2- EBC
- Risk factors of recurrence
- Strategies to improve outcome in high-risk EBC
  - Prolongation of ET
  - Incorporation of other drugs to Anthras-Taxane based CT (ie, capecitabine)
  - m-TOR inhibitors
  - CDK 4/6 inhibitors

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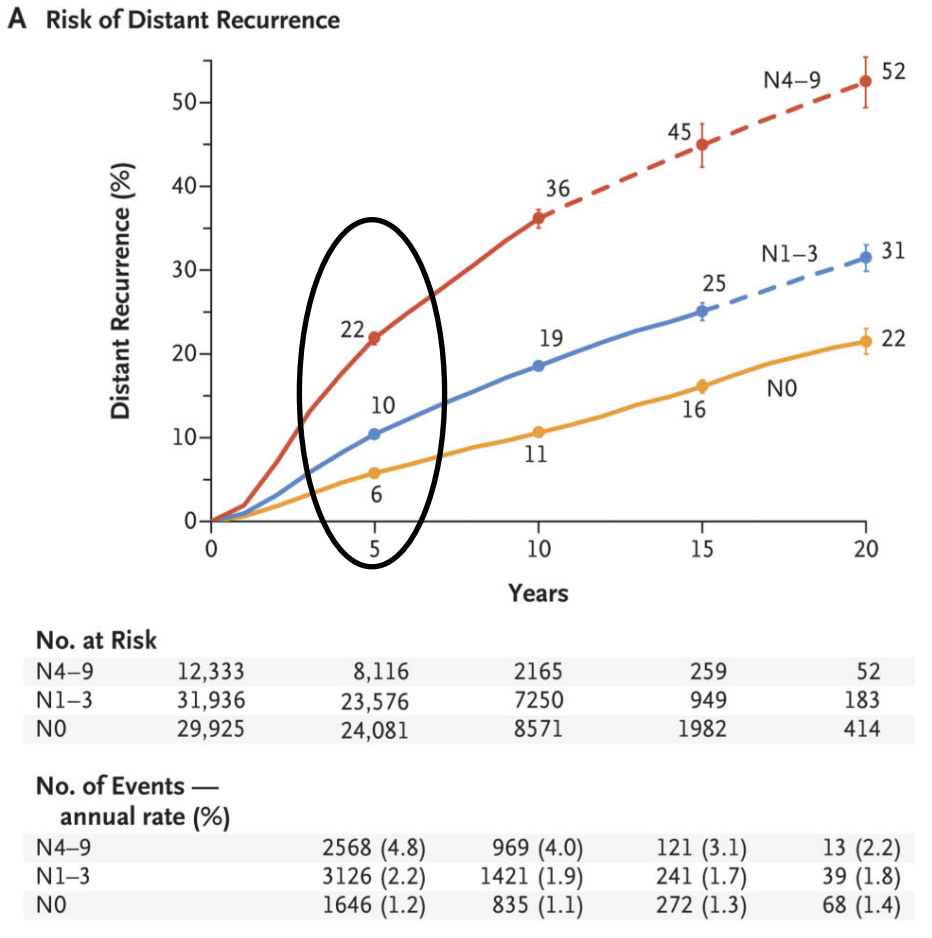
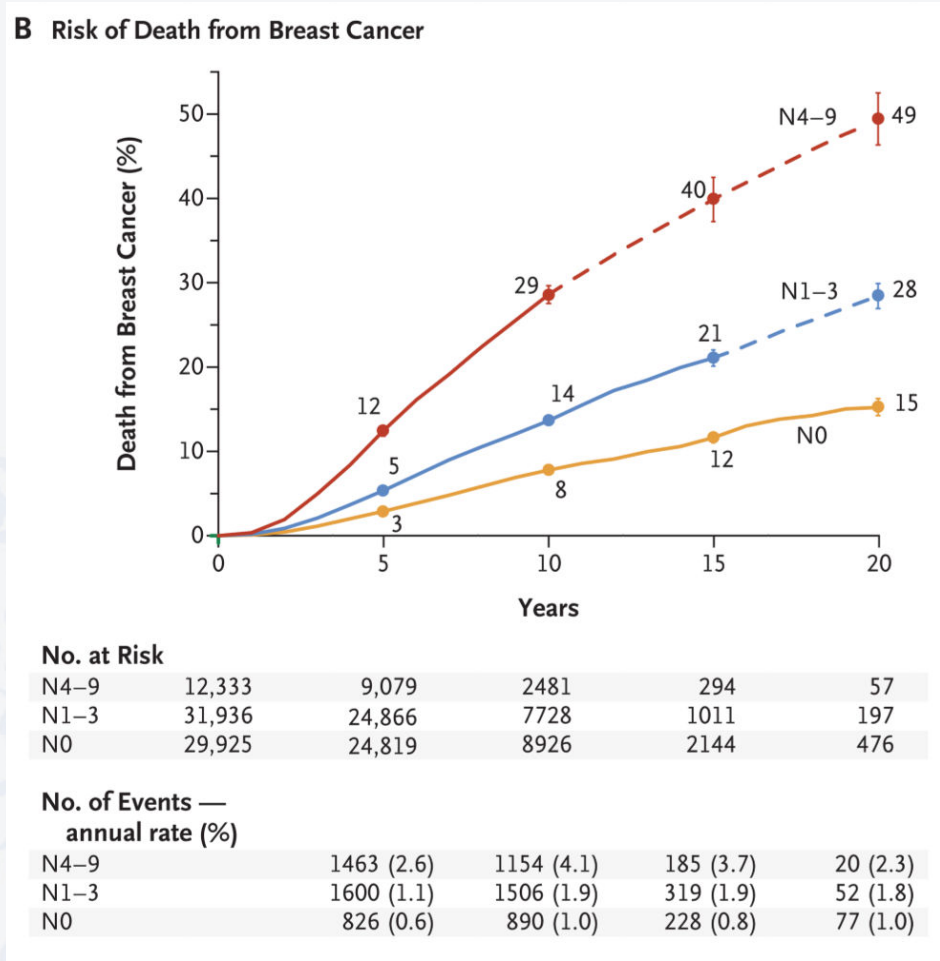
20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

No. of Events — annual rate (%)				
N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)



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N1–3	31,936	24,866	7728	1011	197
N0	29,925	24,819	8926	2144	476

No. of Events — annual rate (%)				
N4–9	1463 (2.6)	1154 (4.1)	185 (3.7)	20 (2.3)
N1–3	1600 (1.1)	1506 (1.9)	319 (1.9)	52 (1.8)
N0	826 (0.6)	890 (1.0)	228 (0.8)	77 (1.0)

Hongchao Pan, N Engl J Med 2017

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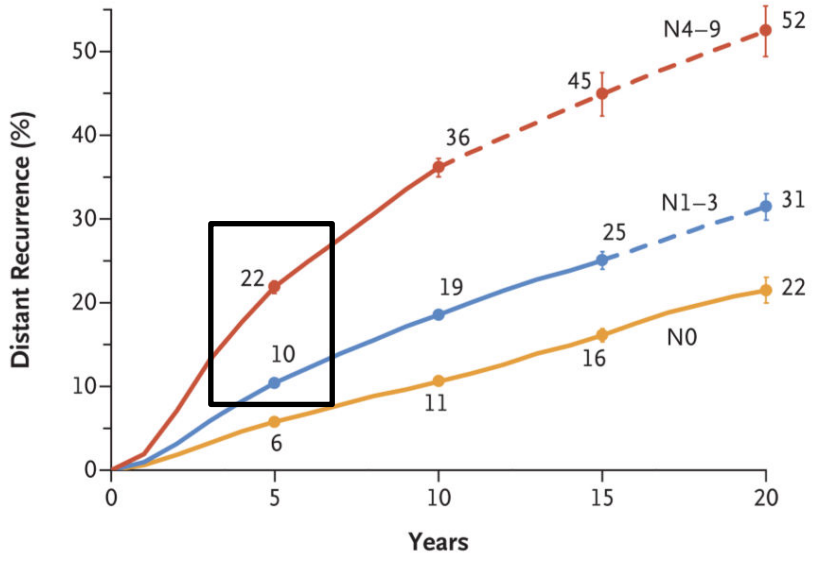
20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

The risk of distant recurrence was strongly correlated with the original nodal status

A Risk of Distant Recurrence



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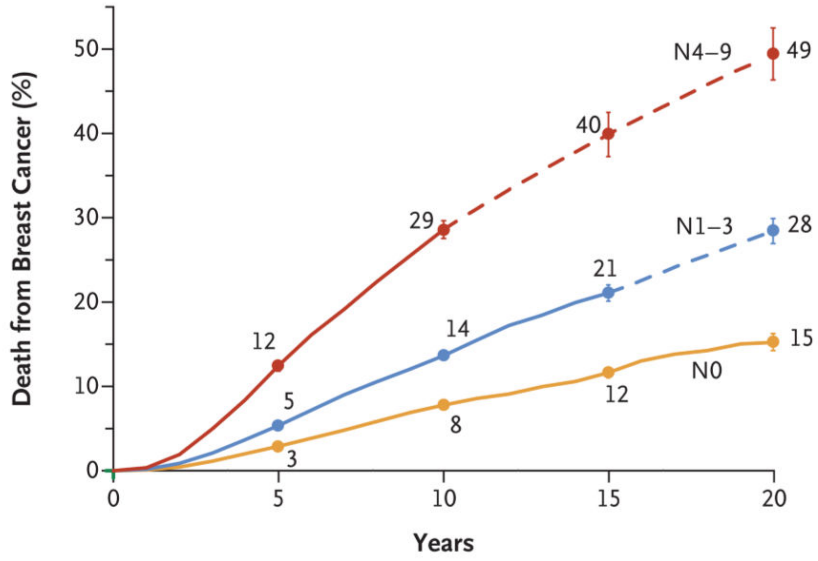
B Risk of Death from Breast Cancer



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Hongchao Pan, N Engl J Med 2017

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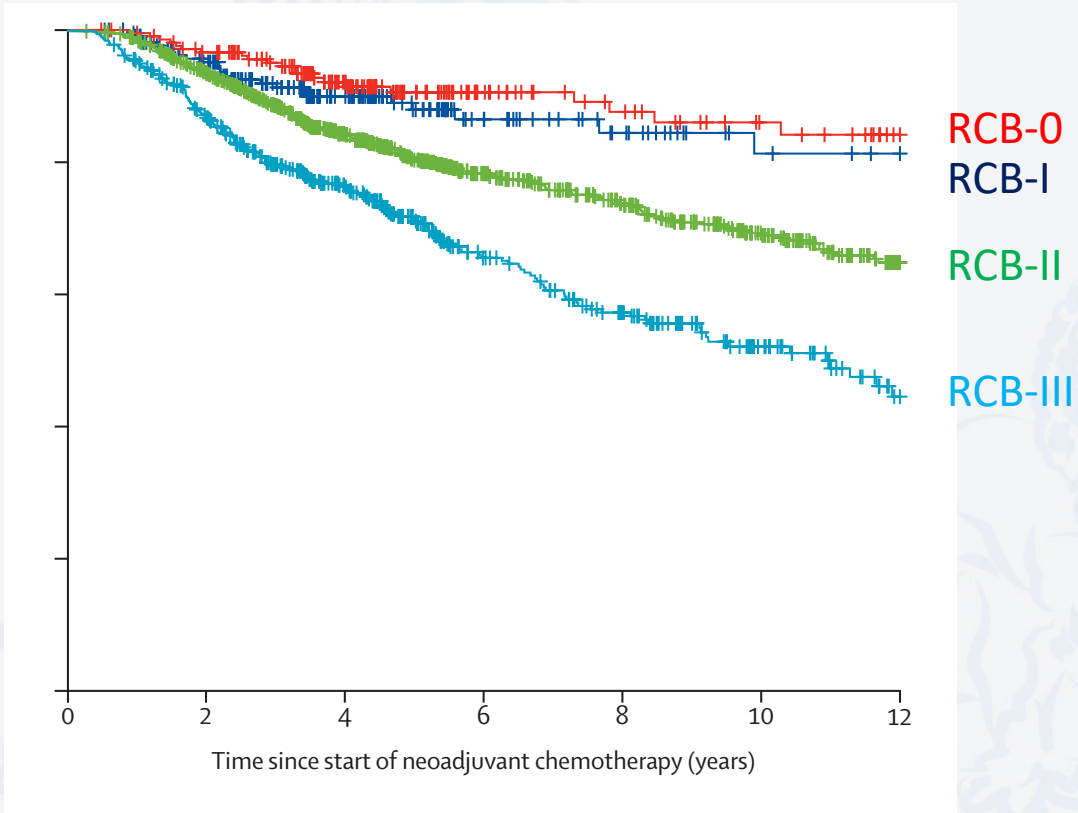
Event Free Survival (EFS) by Residual Cancer Burden (RCB) in HR + HER2 – Breast Cancer

THE LANCET Oncology

Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients

EFS by RCB in HR + HER2 – BC (n=1957)

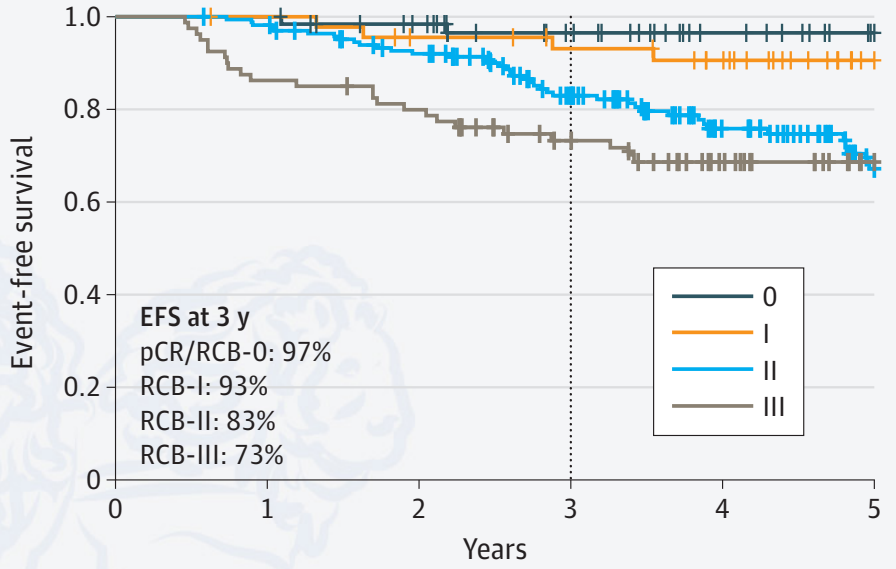


Yau C, Lancet Oncol 2021

JAMA Oncology | Original Investigation

Assessment of Residual Cancer Burden and Event-Free Survival in Neoadjuvant Treatment for High-risk Breast Cancer
An Analysis of Data From the I-SPY2 Randomized Clinical Trial

EFS by RCB in HR + HER2 – BC

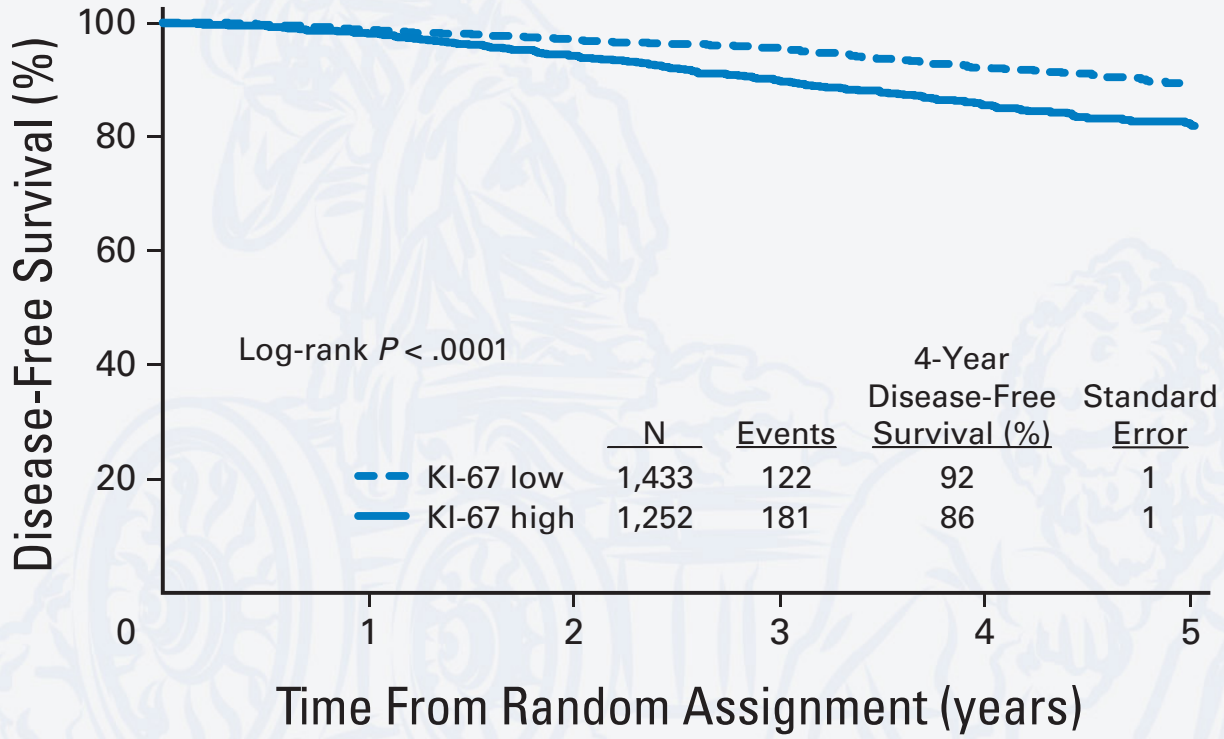


No. at risk						
0	64	64	57	45	33	24
I	46	45	41	38	33	18
II	167	163	146	112	72	41
III	80	69	63	49	34	20

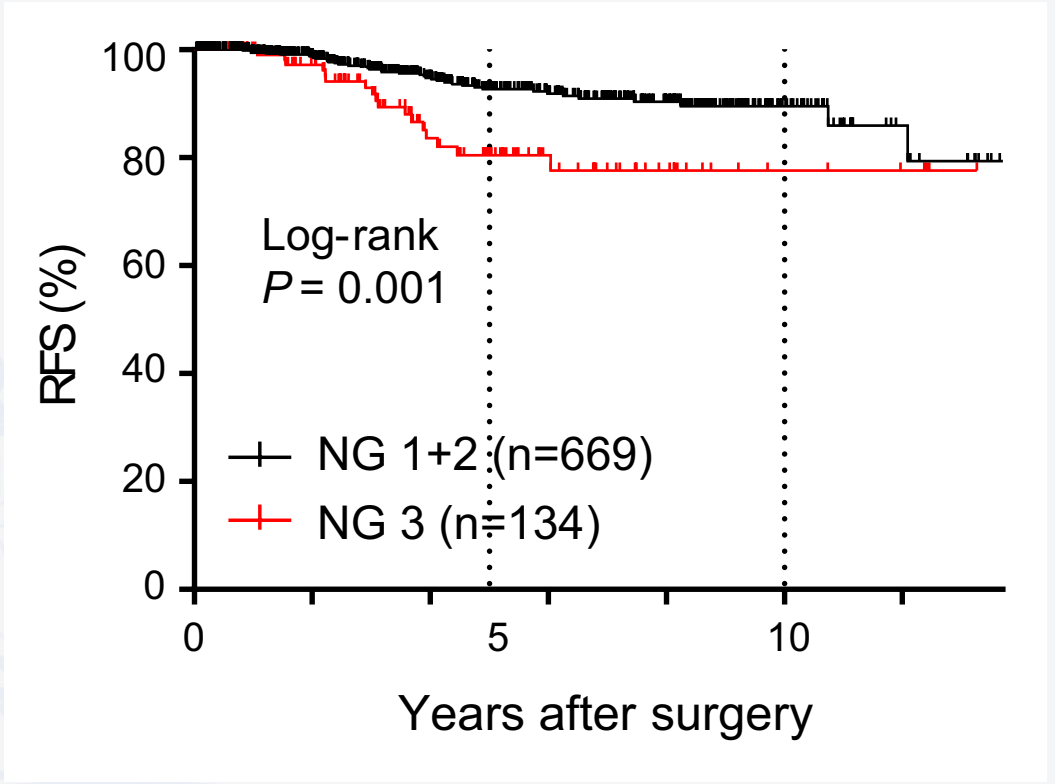
W. Fraser Symmans. JAMA Oncol 2021

Pathologic prognostic factors in Early Breast Cancer

DFS by central Ki-67 expression levels



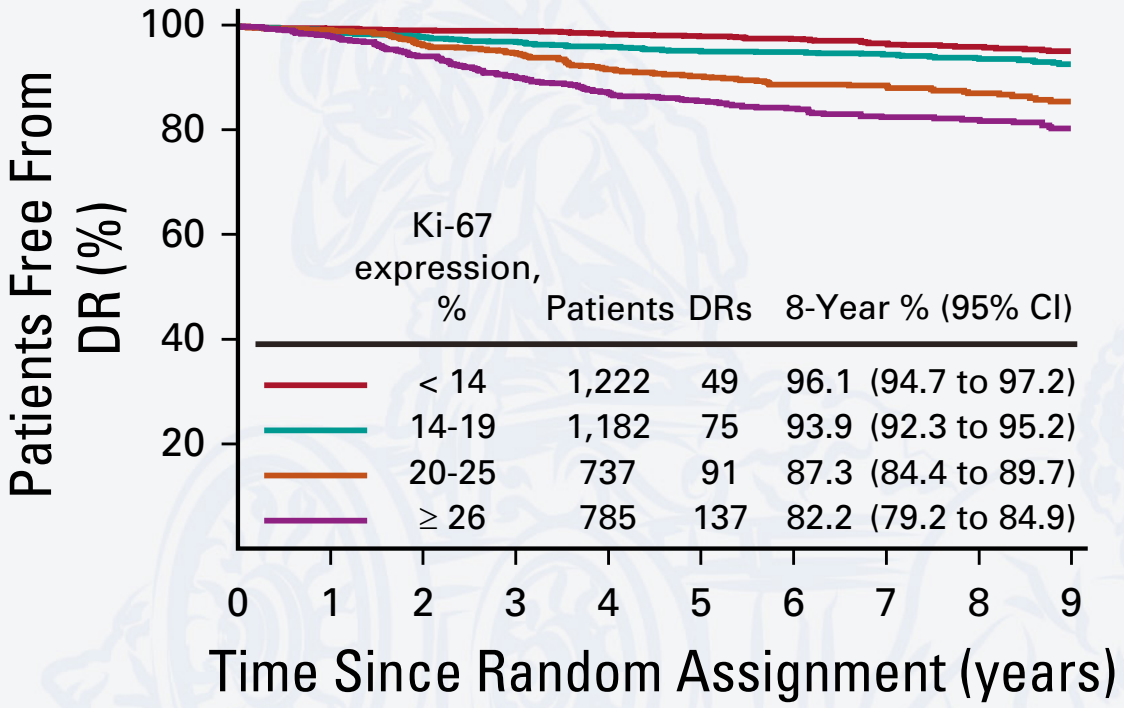
RFS by nuclear grade



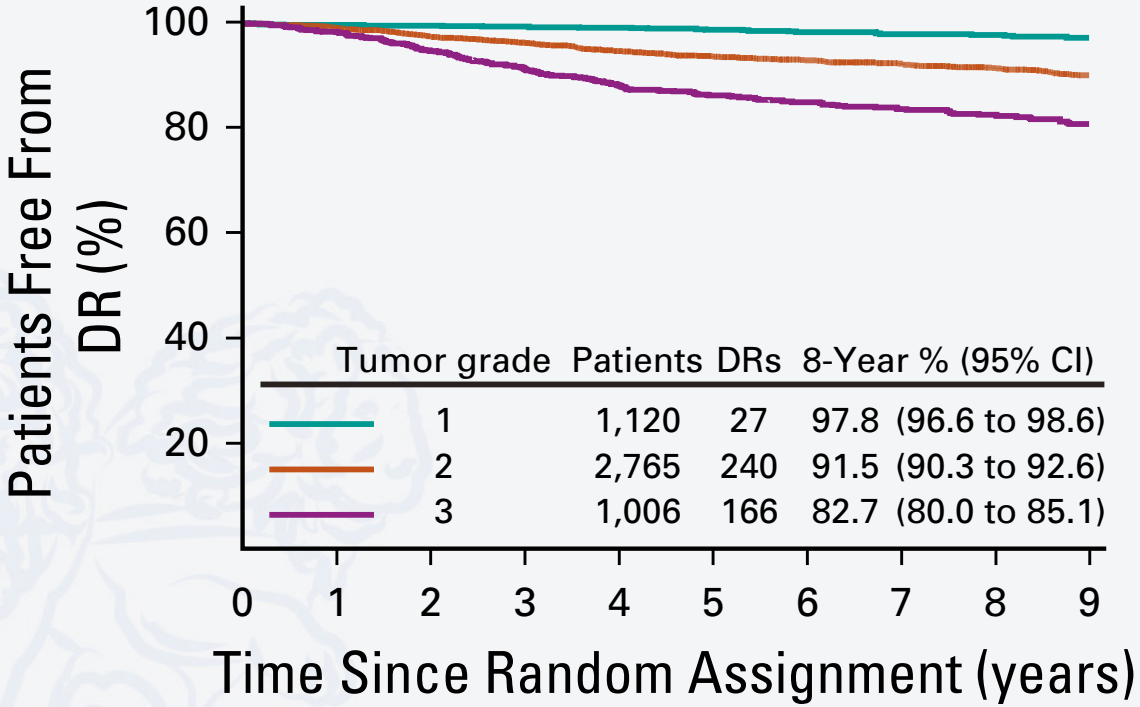
Viale G, J Clin Oncol 2008; Oshiro C, Breast Cancer 2020

Pathologic prognostic factors in Early Breast Cancer

Distant Recurrence by Ki-67 expression levels



Distant Recurrence by grade



Pagani O, J Clin Oncol 2020

XXIV Simposio de Revisiones en Cáncer
"Tratamiento médico del cáncer en el año 2022"

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Combined Use of Clinical and Pathologic Staging Variables to Define Outcomes for Breast Cancer Patients Treated With Neoadjuvant Therapy

Clinical Stage

Clinical Staging for Breast Cancer

TNM Stage: Select Clinical Stage

Pathologic Stage

Pathologic Staging for Breast Cancer

TNM Stage: Select Pathologic Stage

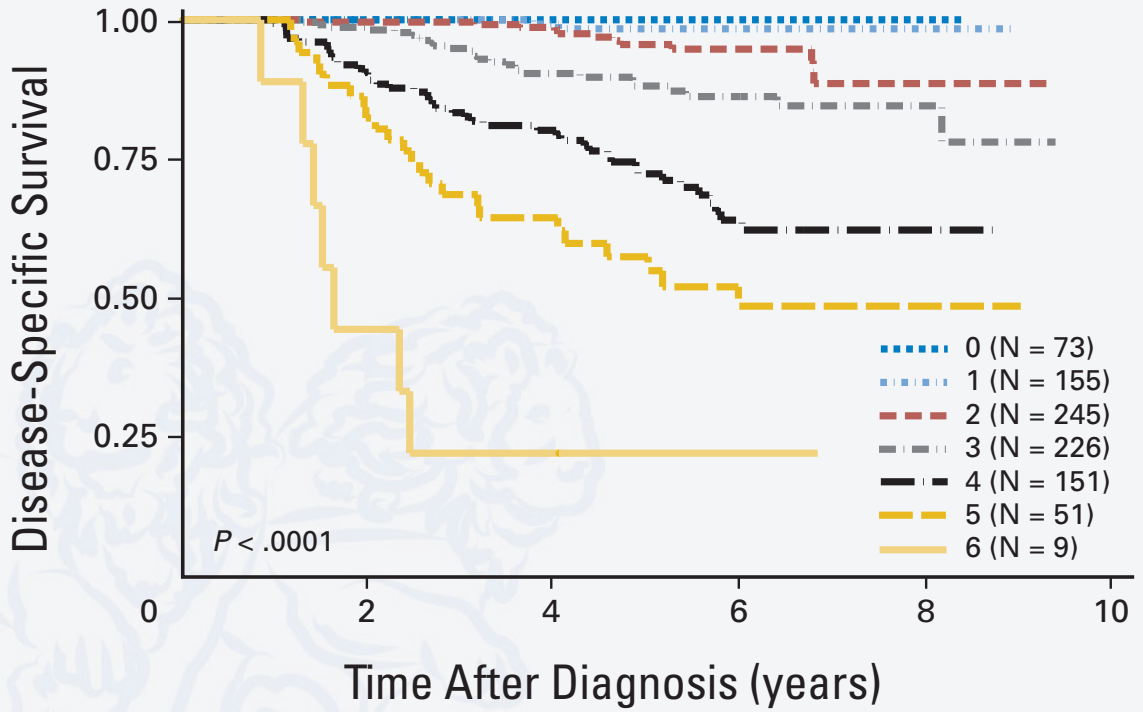
Estrogen Receptor Status

Select Estrogen Receptor Status

Nuclear Grade

Select Nuclear Grade

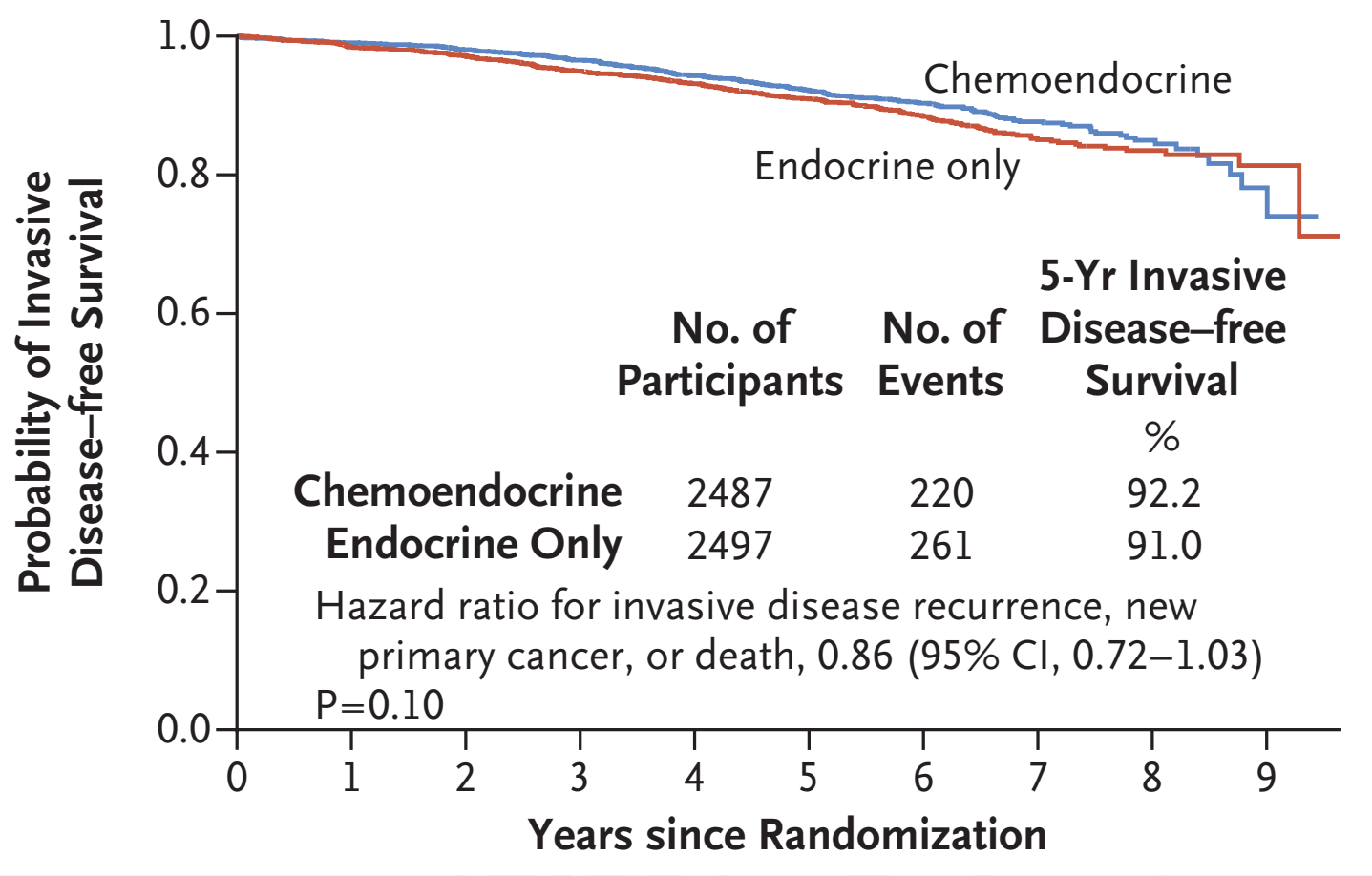
DFS based on CPS + EG score



Jacqueline S. Jeruss, JCO 2008

Genomic Signatures

IDFS in patients with 1-3 LN and RS ≤ 25 (all patients)
RxPONDER Trial

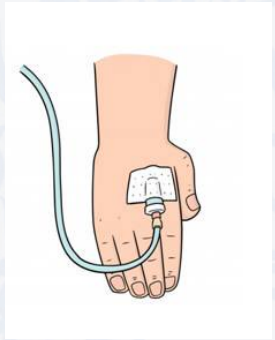


Kalinsky K, N Engl J Med 2021

Risk factors of recurrence

Definition of high risk is critical in the success of escalation clinical trials

- Standard Clinical & Pathological features
- Response to neoadjuvant therapy
- Gene Expression Signatures



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  - Prolongation of ET
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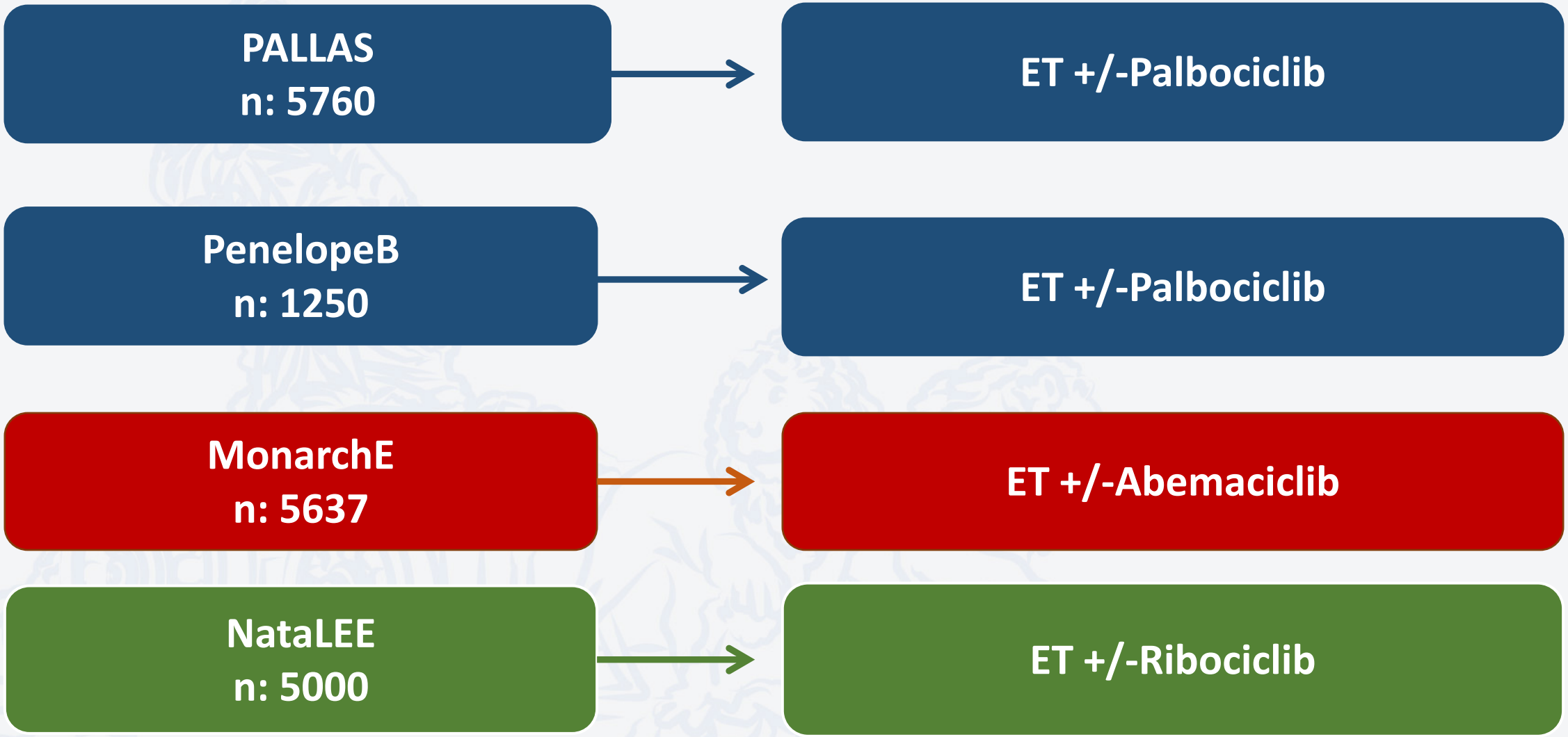
  - m-TOR inhibitors
  - **CDK 4/6 inhibitors**

iCDK 4/6 Adjuvant Trials



Palbociclib with adjuvant endocrine therapy in EBC (PALLAS)

Eligibility:

- Stage II-III HR+/HER2- breast cancer
- Completion of prior surgery, +/- chemo, RT
- Within 12 mo of diagnosis
- Within 6 mo of starting adjuvant endocrine treatment
- FFPE tumor block submitted

N=5,600

Stratification:

- **Stage** (IIA vs IIB/III)
- **Chemotherapy** (yes vs no)
- **Age** (≤50 vs >50)
- **Geographic region** (N. America vs Europe vs Other)

RANDOMIZE

1:1

Arm A
Palbociclib x 2 years
(125 mg qd, 3 wks on/1 wk off)
+
Endocrine Treatment*

Arm B
Endocrine Treatment

* Aromatase inhibitor or tamoxifen, +/- LHRH agonist

Primary Endpoint: invasive Disease-Free Survival (iDFS)

Target HR: 0.75; 5,600 patients provides 85% power, with a 1-sided α=0.025
First IA (197 event) Second IA (313 event) Final A 469 event

Mayer E. ESMO 2020

PALLAS: patients characteristic

- The majority had higher stage disease and had received prior chemotherapy.

- **58·7% had high clinical risk disease, described as:**
  - **≥4 nodes involved (≥N2), or**
  - **1-3 nodes with either T3/T4 and/or grade 3 disease.**

Variable	Palbociclib + ET (N=2,883)	ET (N=2,877)
Age (y) – median (range)	52 (25 – 90)	52 (22 – 85)
Stage		
IIA	504 (17·5%)	509 (17·7%)
IIB	968 (33·6%)	951 (33·1%)
III	1402 (48·6%)	1408 (48·9%)
T-Stage		
T0/T1/Tis/TX	557 (19·3%)	500 (17·4%)
T2	1603 (55·6%)	1636 (56·9%)
T3/T4	722 (25·0%)	741 (25·8%)
N-Stage		
N0	367 (12·7%)	383 (13·3%)
N1	1427 (49·5%)	1415 (49·2%)
N2	703 (24·4%)	709 (24·6%)
N3	385 (13·4%)	370 (12·9%)
Histologic Grade		
G1	300 (10·4%)	313 (10·9%)
G2	1622 (56·3%)	1658 (57·6%)
G3	836 (29·0%)	767 (26·7%)
Prior Chemotherapy	2384 (82·7%)	2370 (82·4%)
Initial Adjuvant Endocrine Therapy		
Aromatase inhibitor	1954 (67·8%)	1918 (66·7%)
Tamoxifen	923 (32·0%)	949 (33·0%)
Concurrent Adjuvant LHRH Agonist	532 (18·5%)	604 (21.1%)

Mayer E. ESMO 2020

PALLAS: safety and tolerability

Adverse Events, incidence ≥ 15%						
Adverse Event	**Palbociclib + ET (N=2,840)**			**ET (N=2,903)**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Any adverse event	2822 (99·4%)	1897 (66·8%)	159 (5·6%)	2571 (88·6%)	400 (13·8%)	24 (0·8%)
Neutropenia	2354 (82·9%)	1620 (57·0%)	122 (4·3%)	139 (4·8%)	11 (0·4%)	0
Leukopenia	1550 (54·6%)	843 (29·7%)	14 (0·5%)	213 (7·3%)	3 (0·1%)	0
Fatigue	1150 (40·5%)	60 (2·1%)	0	546 (18·8%)	10 (0·3%)	0
Arthralgia	992 (34·9%)	30 (1·1%)	0	1207 (41·6%)	31 (1·1%)	0
Upper respiratory tract infection	805 (28·3%)	32 (1·1%)	0	453 (15·6%)	3 (0·1%)	0
Hot flush	693 (24·4%)	7 (0·2%)	0	838 (28·9%)	7 (0·2%)	0
Anaemia	664 (23·4%)	13 (0·5%)	0	157 (5·4%)	4 (0·1%)	0
Thrombocytopenia	609 (21·4%)	25 (0·9%)	1 (0·0%)	49 (1·7%)	1 (0·0%)	0
Nausea	543 (19·1%)	8 (0·3%)	0	240 (8·3%)	4 (0·1%)	0
Alopecia	496 (17·5%)	0	0	144 (5·0%)	0	0
Diarrhoea	468 (16·5%)	21 (0·7%)	0	145 (5·0%)	5 (0·2%)	0
Headache	435 (15·3%)	7 (0·2%)	0	322 (11·1%)	7 (0·2%)	0

42.2% had discontinue prematurely (due AE 64.2%)

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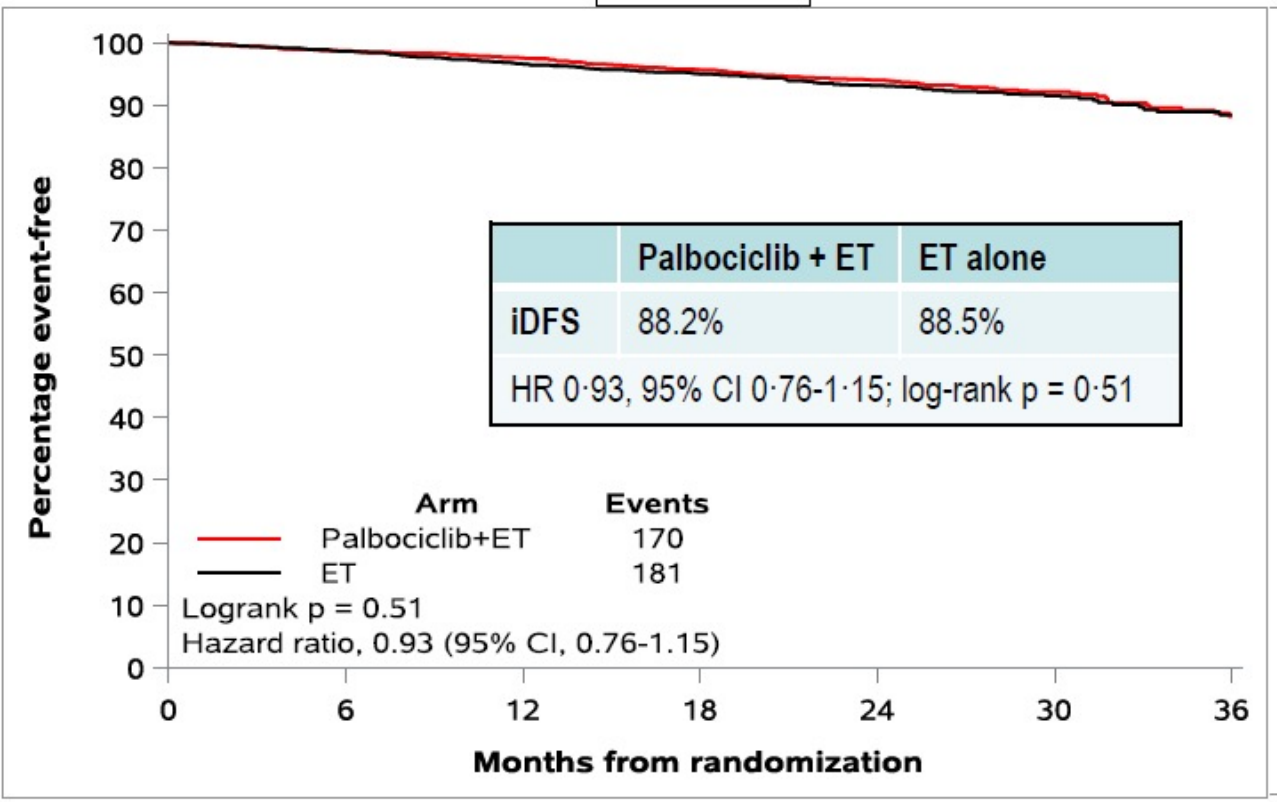
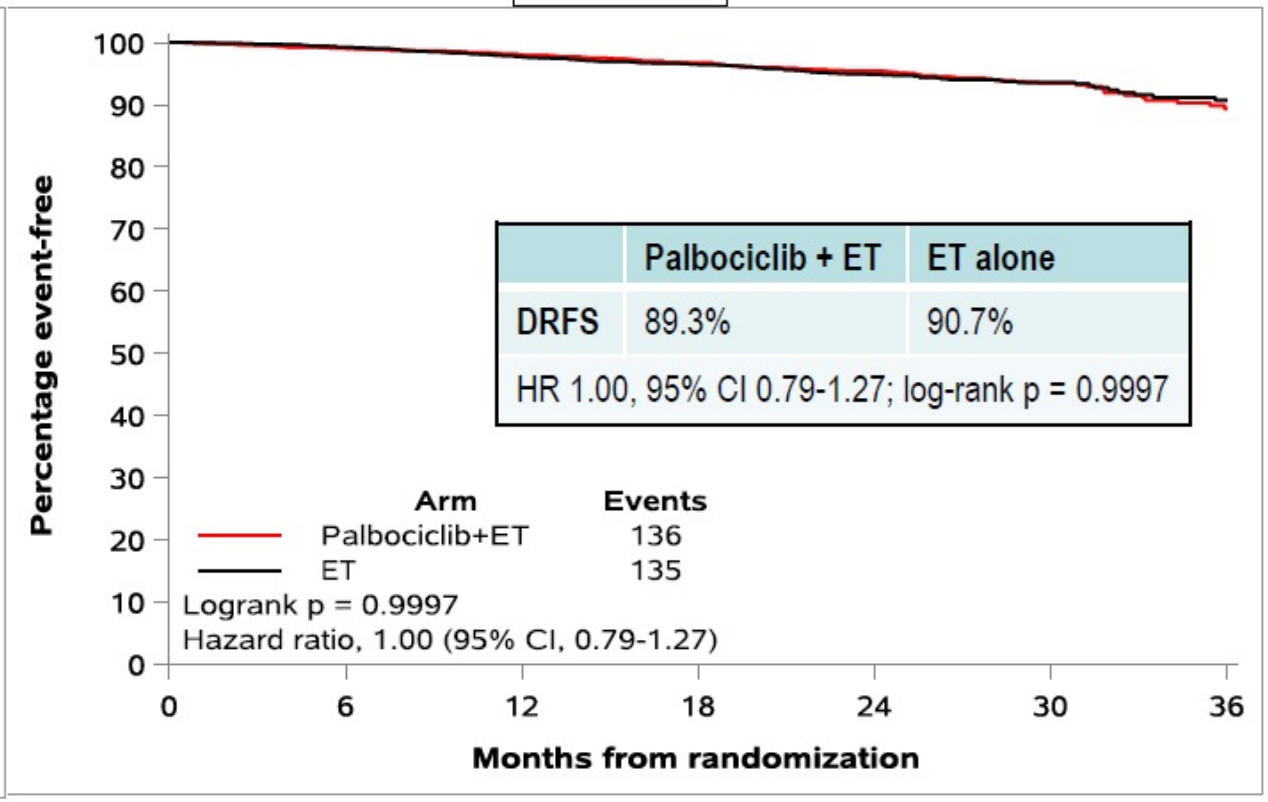
PALLAS: Primary Endpoint iDFS

iDFS



DRFS



At a median follow-up of 23.7 months, no significant difference in either 3-year iDFS or DRFS was observed

Mayer E. ESMO 2020

PALLAS: Conclusions

- The addition of **palbociclib** to adjuvant ET **did not prolong** iDFS compared to ET alone in patients with stage II-III HR+/HER2-

Mayer E. ESMO 2020

Palbociclib and adjuvant ET for high-risk HR+/HER2- EBC after neoadjuvant Chemo (PENELOPE-B)

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

Target HR: 0.685; 85% power, with a 2-sided α=0.05
First IA (290 event) Second IA (194 event) Final level 0.0463

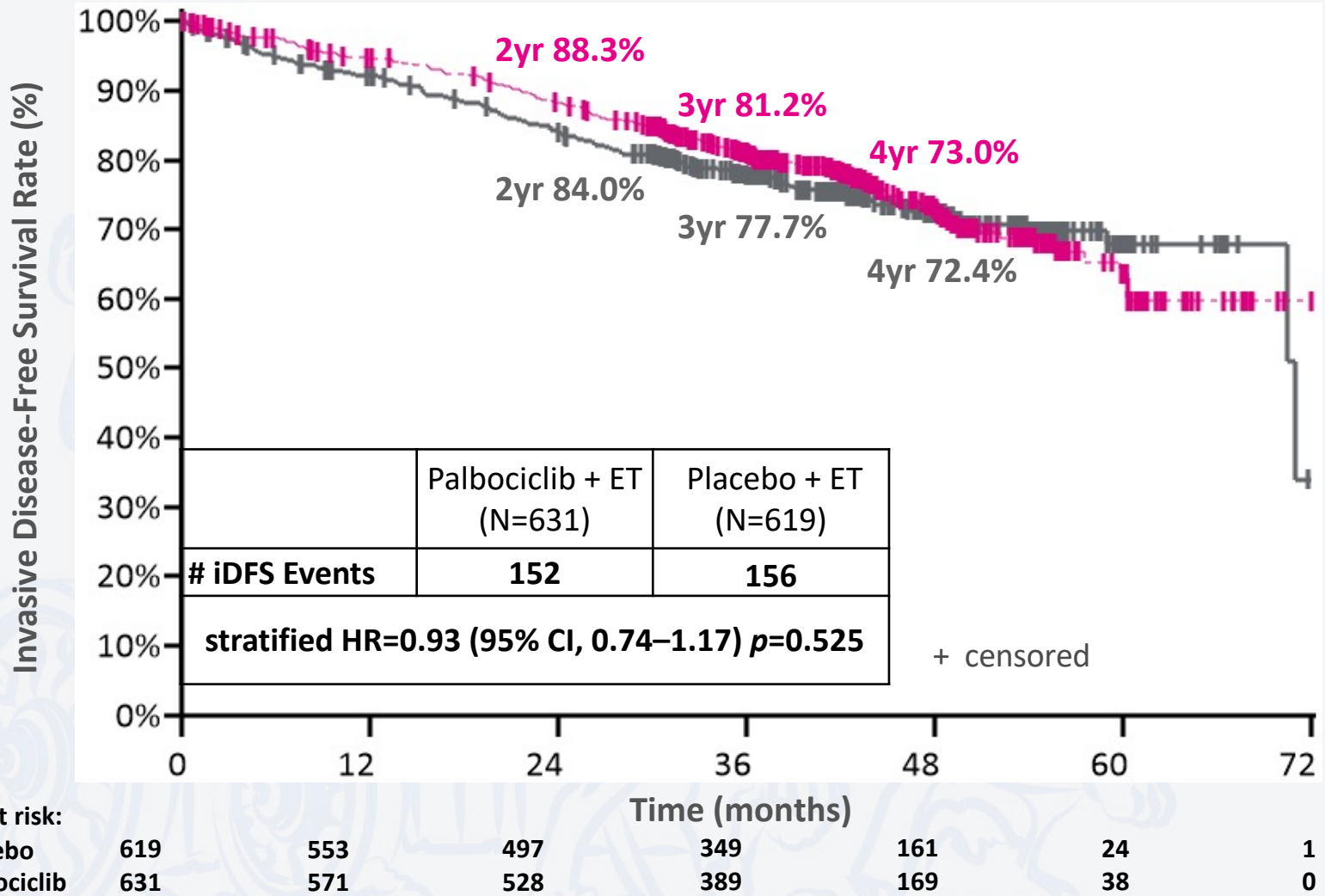
Loibls S. SABCS 2020

Penelope-B: Mainline characteristics

Parameter	Category	Palbociclib (N=631) N (%*)	Placebo (N=619) N (%*)	Overall (N=1250) N (%*)
Age	median (range)	49 (22.76)	48 (19.79)	49 (19.79)
Age, years	≤50	353 (55.9)	348 (56.2)	701 (56.1)
Histological lymph node status at surgery	ypN 0-1	310 (49.1)	310 (50.1)	620 (49.6)
	ypN 2-3	321 (50.9)	309 (49.9)	630 (50.4)
Ki-67%, central pathology	>15%	161 (25.5)	158 (25.5)	319 (25.5)
CPS-EG score	2 and ypN+	253 (40.1)	255 (41.2)	508 (40.6)
	≥3	378 (59.9)	364 (58.8)	742 (59.4)
Tumor stage at surgery	ypT0-1	238 (37.7)	208 (33.7)	446 (35.7)
	ypT2-3	368 (58.3)	389 (62.9)	757 (60.6)
	ypT4	25 (4.0)	21 (3.4)	46 (3.7)
Histological type	lobular	58 (9.2)	52 (8.5)	110 (8.8)
Grading	G3	294 (46.7)	297 (48.1)	591 (47.4)
Ovarian ablation		108 (17.1)	113 (18.3)	221 (17.7)
Endocrine therapy Tamoxifen	overall	314 (49.8)	308 (49.8)	622 (49.8)

Loibls S. SABCS 2020

Penelope-B: Primary Endpoint iDFS



	Palbociclib + ET (N=631)	Placebo + ET (N=619)
# iDFS Events	152	156
stratified HR=0.93 (95% CI, 0.74–1.17) *p*=0.525		

Patients at risk:							
Placebo	619	553	497	349	161	24	1
Palbociclib	631	571	528	389	169	38	0

Median Follow-Up 42.8 Months

19.5% had discontinue prematurely

Loibls S. SABCS 2020

Penelope-B: Conclusion

- The addition of **palbocicilib** to adjuvant ET **did not improve** iDFS compared to ET alone in patients HR+, HER2- EBC at high-risk of relapse after NACT

Loibls S. SABCS 2020

Abemaciclib with adjuvant ET for HR+/HER2- Node+, high-risk EBC (monarchE)

HR+, HER2-, high risk early breast cancer

High risk defined as:

- ≥4 positive axillary lymph nodes (ALN) OR
- 1-3 ALN and at least 1 of the below:
  - Tumor size ≥5 cm
  - Histologic grade 3
  - Centrally tested Ki67 ≥20%

N = 5637[a]

R 1:1

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

Abemaciclib (150mg twice daily for up to 2 years[b])
+ Standard of Care Endocrine Therapy
(5 to 10 years as clinically indicated)

Standard of Care Endocrine Therapy[b]
(5 to 10 years as clinically indicated)

Endocrine therapy of physician's choice

Other criteria:
- Women or men
- Pre-/ postmenopausal
- With or without prior adjuvant/neoadjuvant chemotherapy
- No distant metastases

Primary Objective: Invasive disease-free survival (STEEP criteria)
Key Secondary Objectives: Distant relapse-free survival, Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

Target HR: 0.73; 85% power, with a 2-sided α=0.05; 390 events for primary analysis
First IA (323 iDFS, positive study if p<0.264)

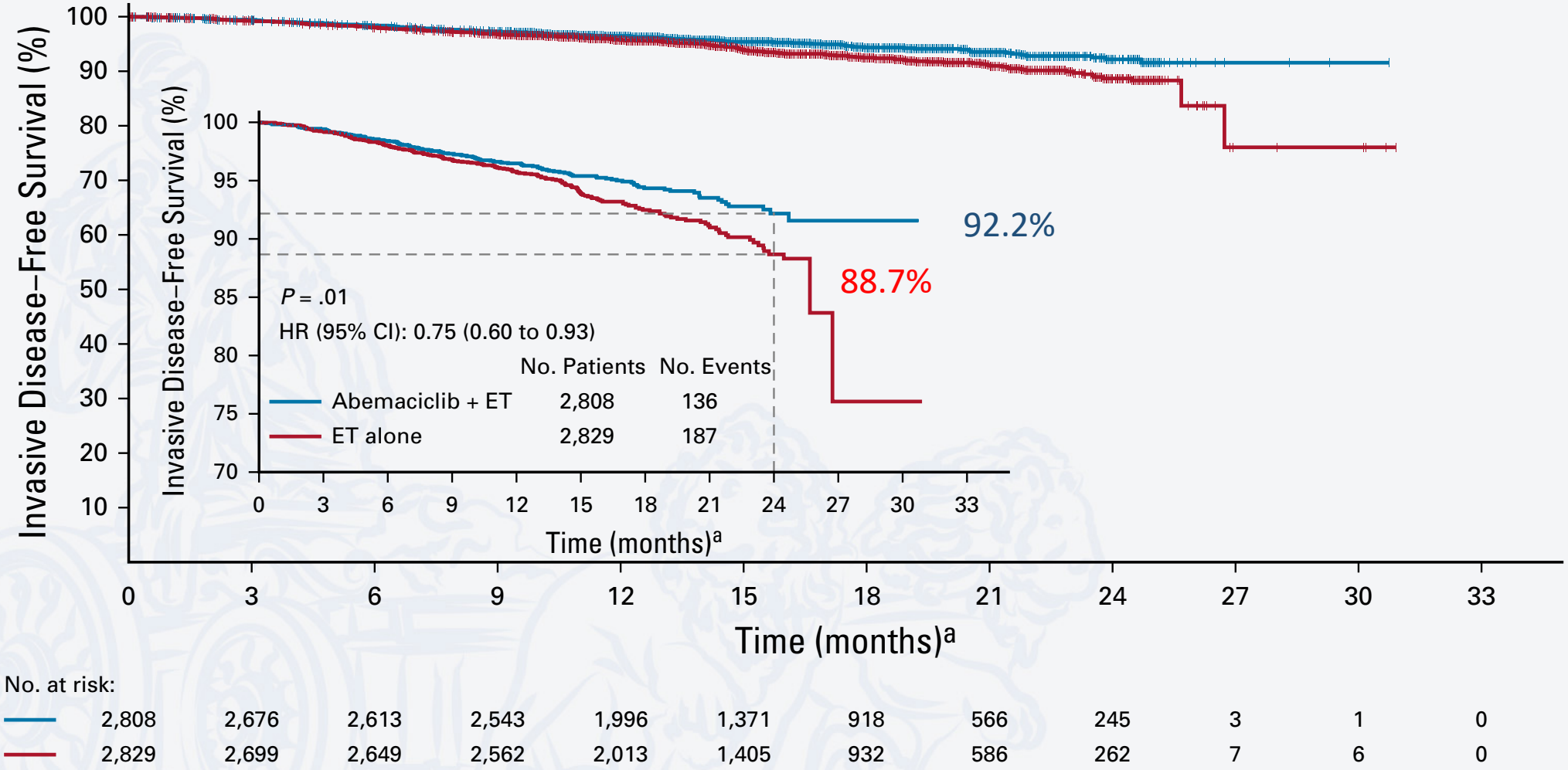
Johnston S. ESMO 2020

monarchE: Patients Characteristics

		Abemaciclib + ET N=2808, %	ET Alone N=2829, %
Age	Median (range)	51 (23-89)	51 (22-86)
Age categories	<65 years	84.4	85.4
Gender	Female	99.3	99.5
Menopausal Status[1]	Premenopausal	43.5	43.5
	Postmenopausal	56.5	56.5
Prior Chemotherapy[1]	Neoadjuvant	37.0	37.0
	Adjuvant	58.5	58.2
	None	4.5	4.7
Baseline ECOG PS	0	85.7	83.8
Pathologic Tumor Size	<2 cm	27.8	27.1
	2 - 5 cm	48.9	50.2
	≥5 cm	21.6	21.6
Number of Positive Lymph Nodes	1-3	39.8	40.4
	≥4	59.9	59.6
Histological Grade	Grade 1	7.4	7.6
	Grade 2	49.0	49.3
	Grade 3	38.7	37.6
Central Ki-67	<20%	33.9	34.4
	≥20%	44.9	43.6
	Unavailable	21.1	21.8

Johnston S. ESMO 2020

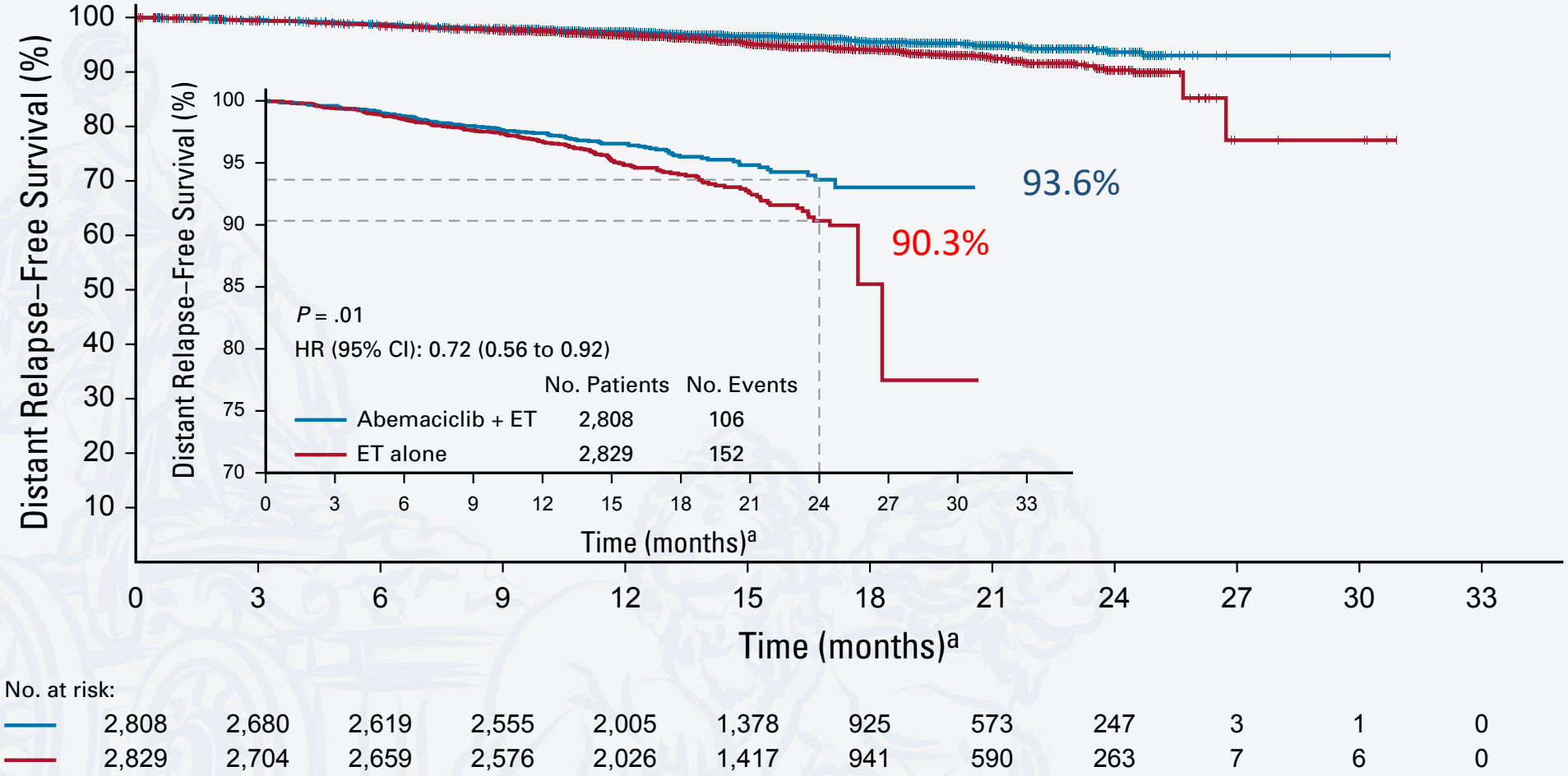
monarch-E: Primary Endpoint iDFS



Two-year IDFS rates were 92.2% (abemaciclib + ET arm) and 88.7% (ET arm): 3.5 absolute difference

Johnston S, JCO 2020

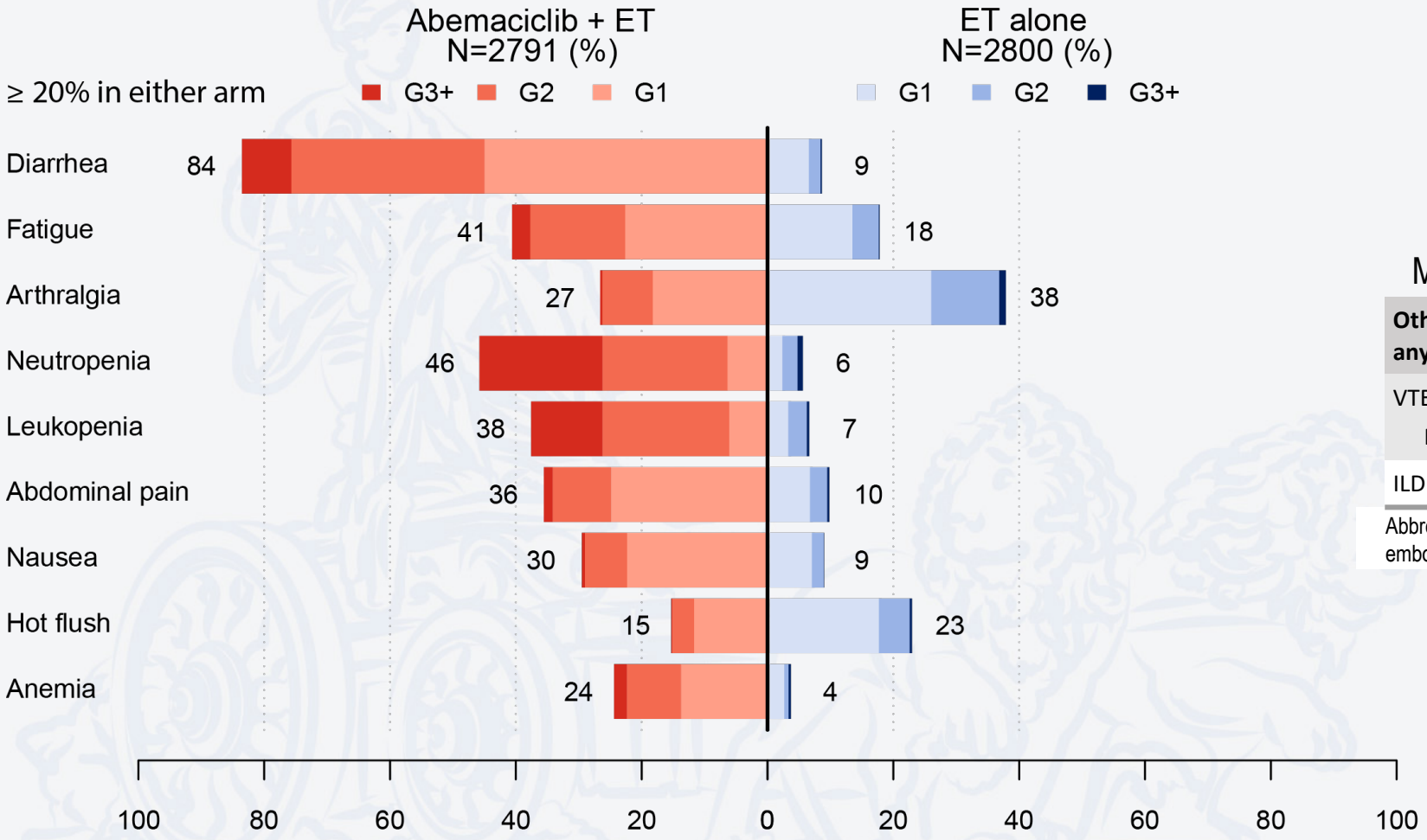
monarchE: Distant Relapse-Free Survival



Two-year DRFS rates were 93.6% (abemaciclib + ET arm) and 90.3% (ET arm): 3.3% absolute difference DRFS benefit consistent accros all prespecified subgroups

Johnston S, JCO 2020

monarchE: Treatment Emergent Adverse Events



Median duration of abemaciclib: 23.7 months

Other events of interest, 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

Abbreviations: VTE = venous thromboembolic event; PE = pulmonary embolism; ILD = Interstitial lung disease

16% treatment discontinuation

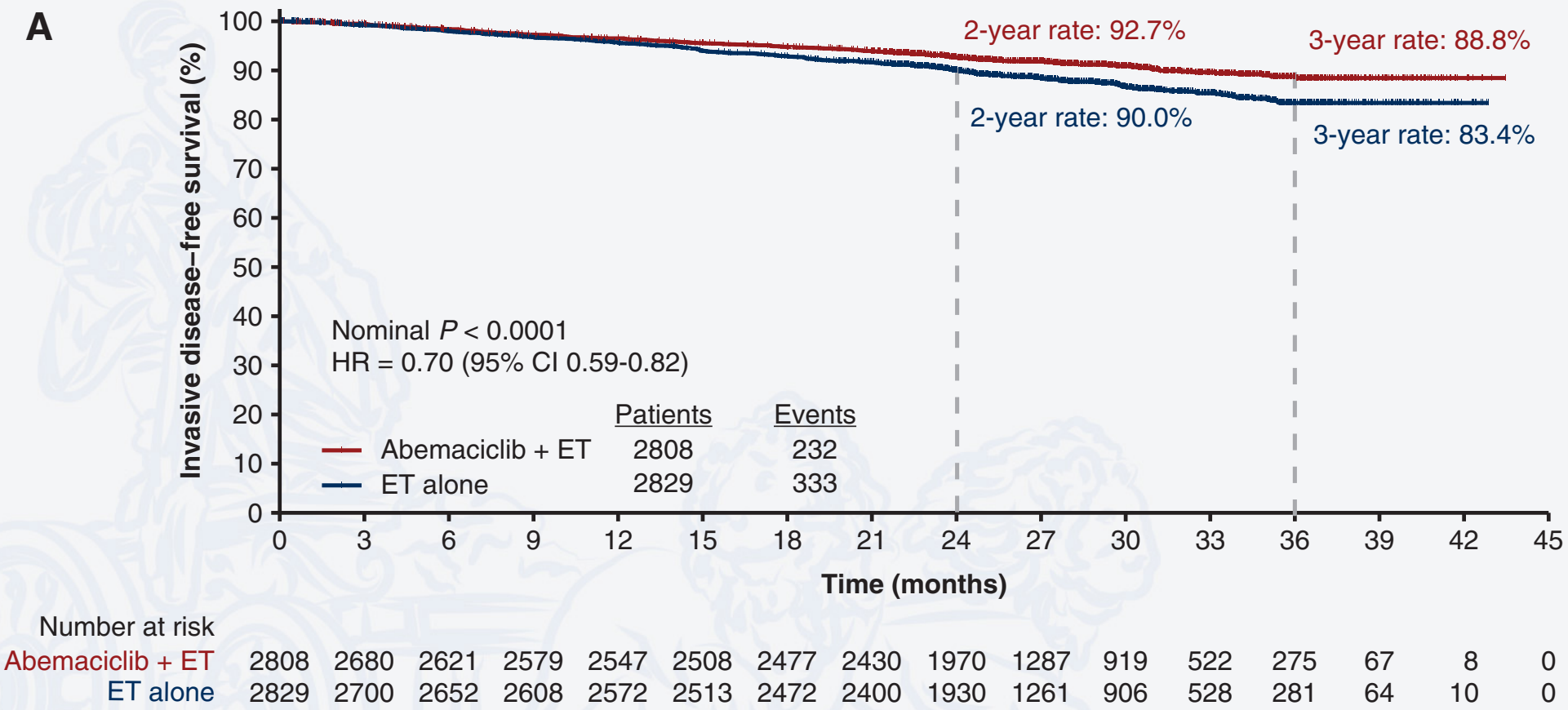
O'Shaughnessy J. ESMO 2021

monarchE: Conclusions

- **Abemaciclib + adjuvant ET** demonstrated clinically meaningful **improvement in IDFS & DRFS** in HR+/HER2- eBC

An additional analysis was conducted in response to regulators, with a data cut-off date on April 1, 2021, at which point most patients had discontinued or completed the study treatment period.

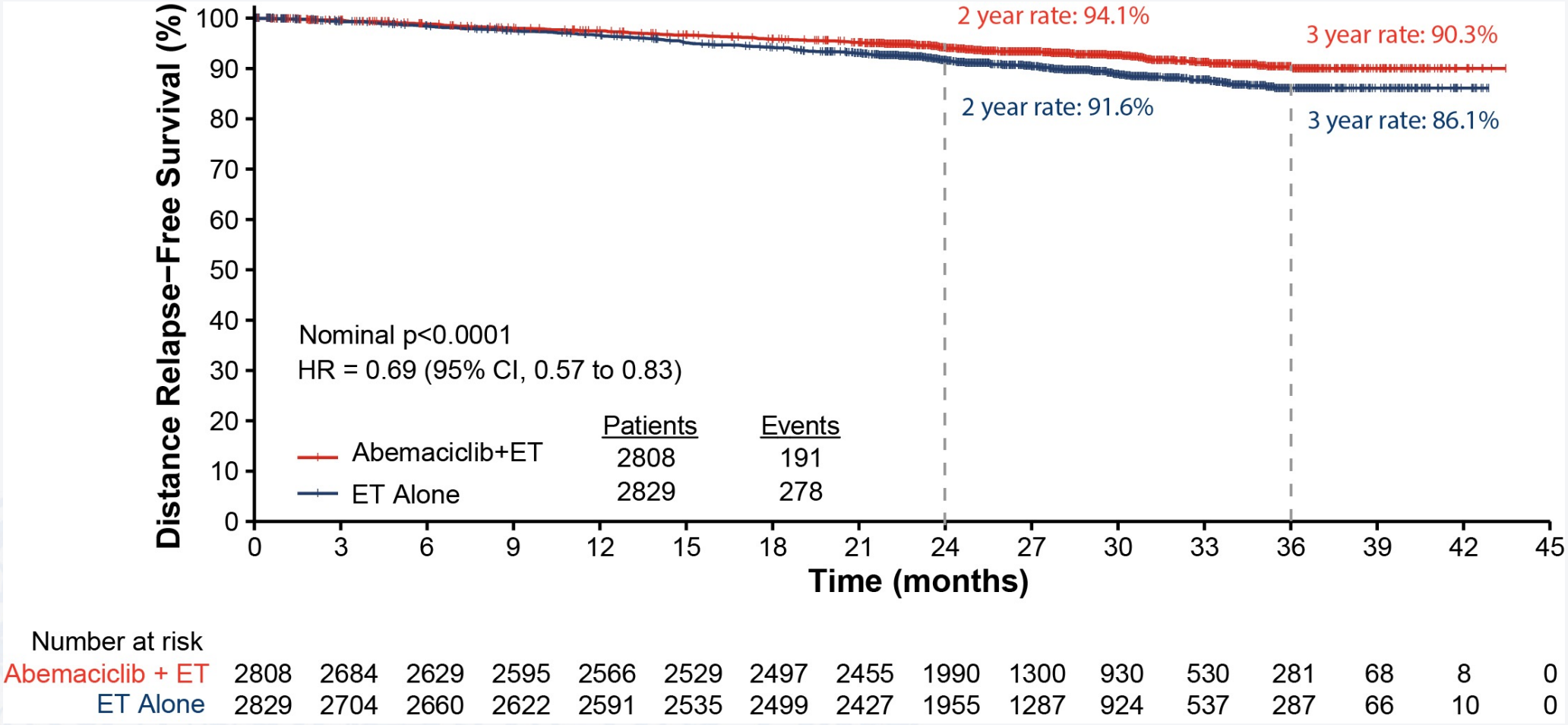
IDFS Benefit Maintained with 27m Follow-up



30.4% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 5.4% at 3 years.

Harbeck N, Ann Oncol 2021

DRFS Benefit Maintained with 27m Follow-up

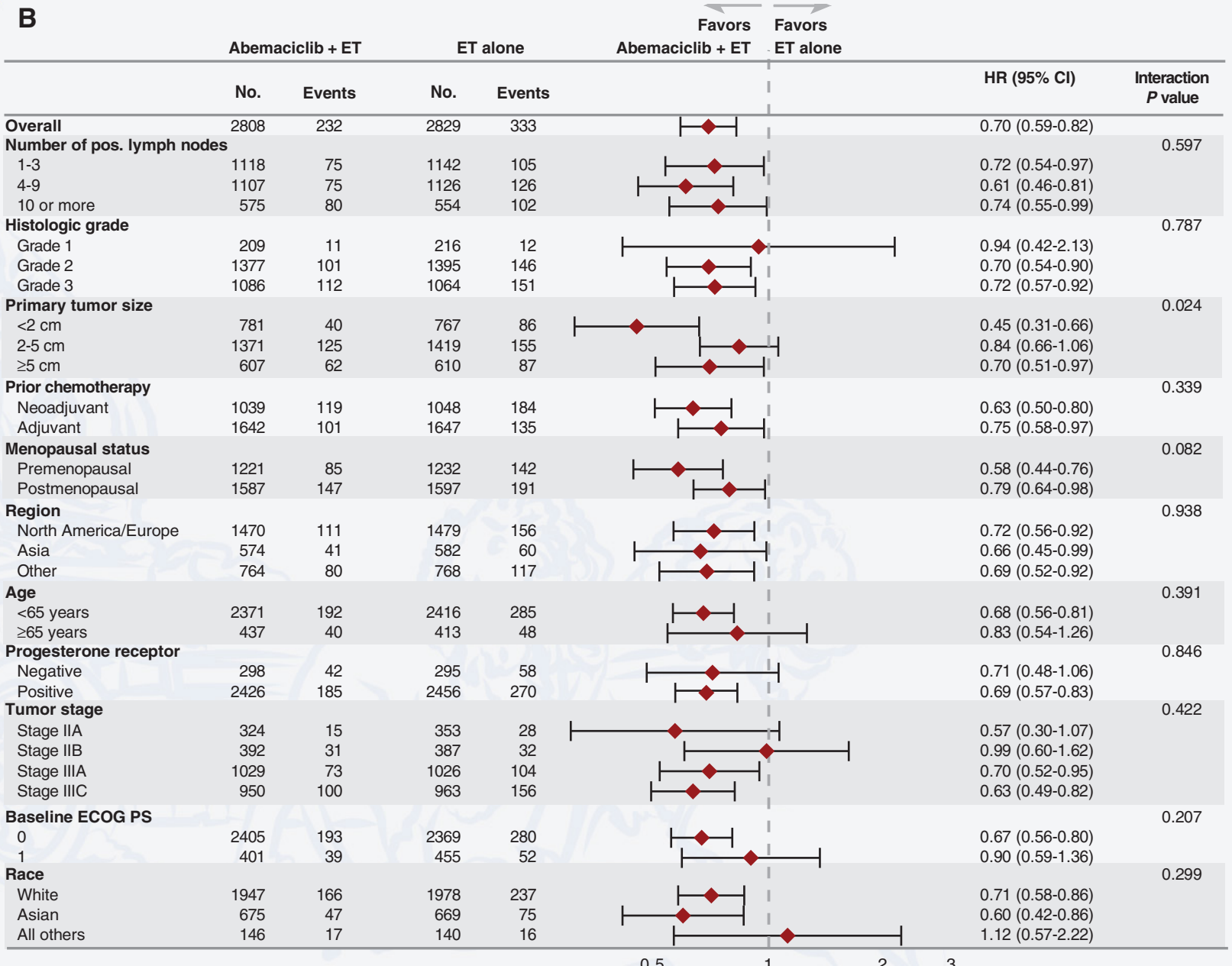


31.3% reduction in the risk of developing a DRFS event.
The absolute difference in DRFS rates between arms was 4.2% at 3 years.

Harbeck N, Ann Oncol 2021

Consistent IDFS treatment benefit in prespecified subgroups

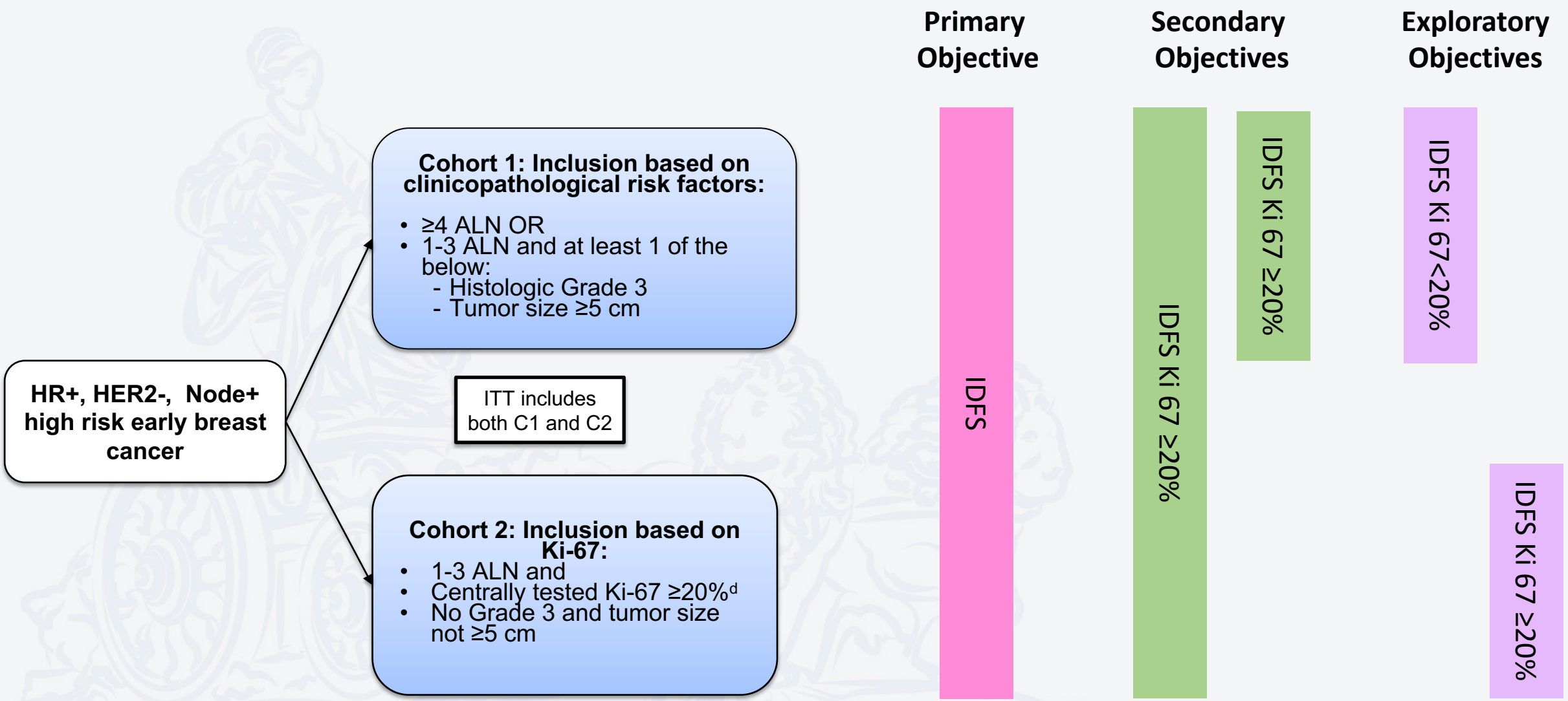
B



	Abemaciclib + ET		ET alone		HR (95% CI)	Interaction *P* value
	No.	Events	No.	Events		
Overall	2808	232	2829	333	0.70 (0.59-0.82)	
Number of pos. lymph nodes						0.597
1-3	1118	75	1142	105	0.72 (0.54-0.97)	
4-9	1107	75	1126	126	0.61 (0.46-0.81)	
10 or more	575	80	554	102	0.74 (0.55-0.99)	
Histologic grade						0.787
Grade 1	209	11	216	12	0.94 (0.42-2.13)	
Grade 2	1377	101	1395	146	0.70 (0.54-0.90)	
Grade 3	1086	112	1064	151	0.72 (0.57-0.92)	
Primary tumor size						0.024
<2 cm	781	40	767	86	0.45 (0.31-0.66)	
2-5 cm	1371	125	1419	155	0.84 (0.66-1.06)	
≥5 cm	607	62	610	87	0.70 (0.51-0.97)	
Prior chemotherapy						0.339
Neoadjuvant	1039	119	1048	184	0.63 (0.50-0.80)	
Adjuvant	1642	101	1647	135	0.75 (0.58-0.97)	
Menopausal status						0.082
Premenopausal	1221	85	1232	142	0.58 (0.44-0.76)	
Postmenopausal	1587	147	1597	191	0.79 (0.64-0.98)	
Region						0.938
North America/Europe	1470	111	1479	156	0.72 (0.56-0.92)	
Asia	574	41	582	60	0.66 (0.45-0.99)	
Other	764	80	768	117	0.69 (0.52-0.92)	
Age						0.391
<65 years	2371	192	2416	285	0.68 (0.56-0.81)	
≥65 years	437	40	413	48	0.83 (0.54-1.26)	
Progesterone receptor						0.846
Negative	298	42	295	58	0.71 (0.48-1.06)	
Positive	2426	185	2456	270	0.69 (0.57-0.83)	
Tumor stage						0.422
Stage IIA	324	15	353	28	0.57 (0.30-1.07)	
Stage IIB	392	31	387	32	0.99 (0.60-1.62)	
Stage IIIA	1029	73	1026	104	0.70 (0.52-0.95)	
Stage IIIC	950	100	963	156	0.63 (0.49-0.82)	
Baseline ECOG PS						0.207
0	2405	193	2369	280	0.67 (0.56-0.80)	
1	401	39	455	52	0.90 (0.59-1.36)	
Race						0.299
White	1947	166	1978	237	0.71 (0.58-0.86)	
Asian	675	47	669	75	0.60 (0.42-0.86)	
All others	146	17	140	16	1.12 (0.57-2.22)	

Harbeck N, Ann Oncol 2021

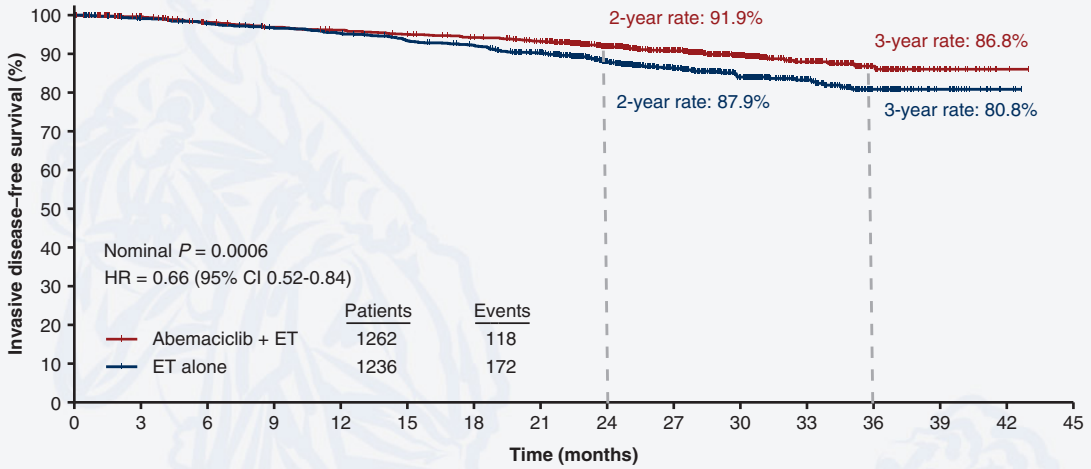
monarchE Study Design



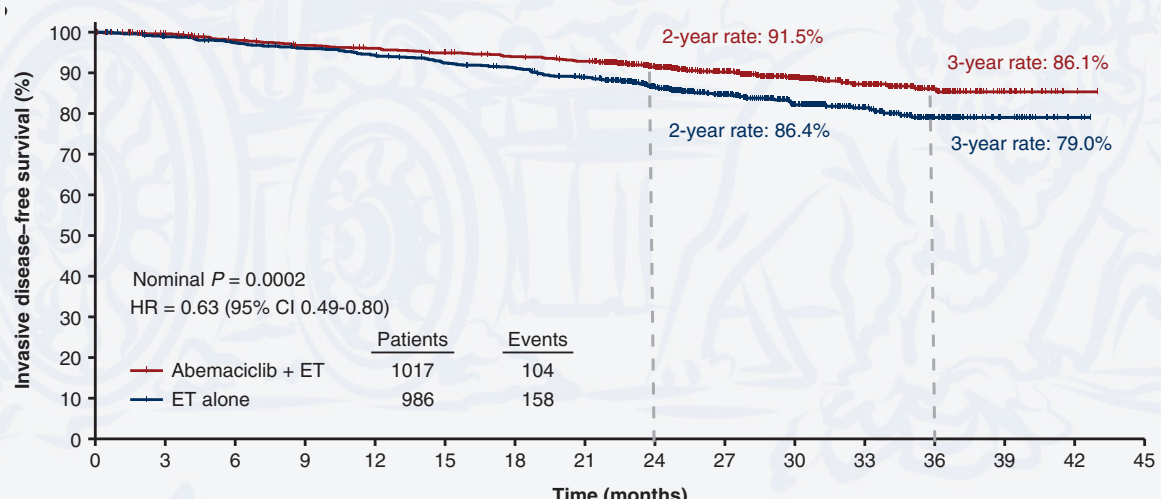
Harbeck N, Ann Oncol 2021

IDFS in ITT Ki-67-high and cohort 1 Ki-67-high populations

IDFS in ITT Ki-67-high



IDFS in cohort 1 Ki-67-high



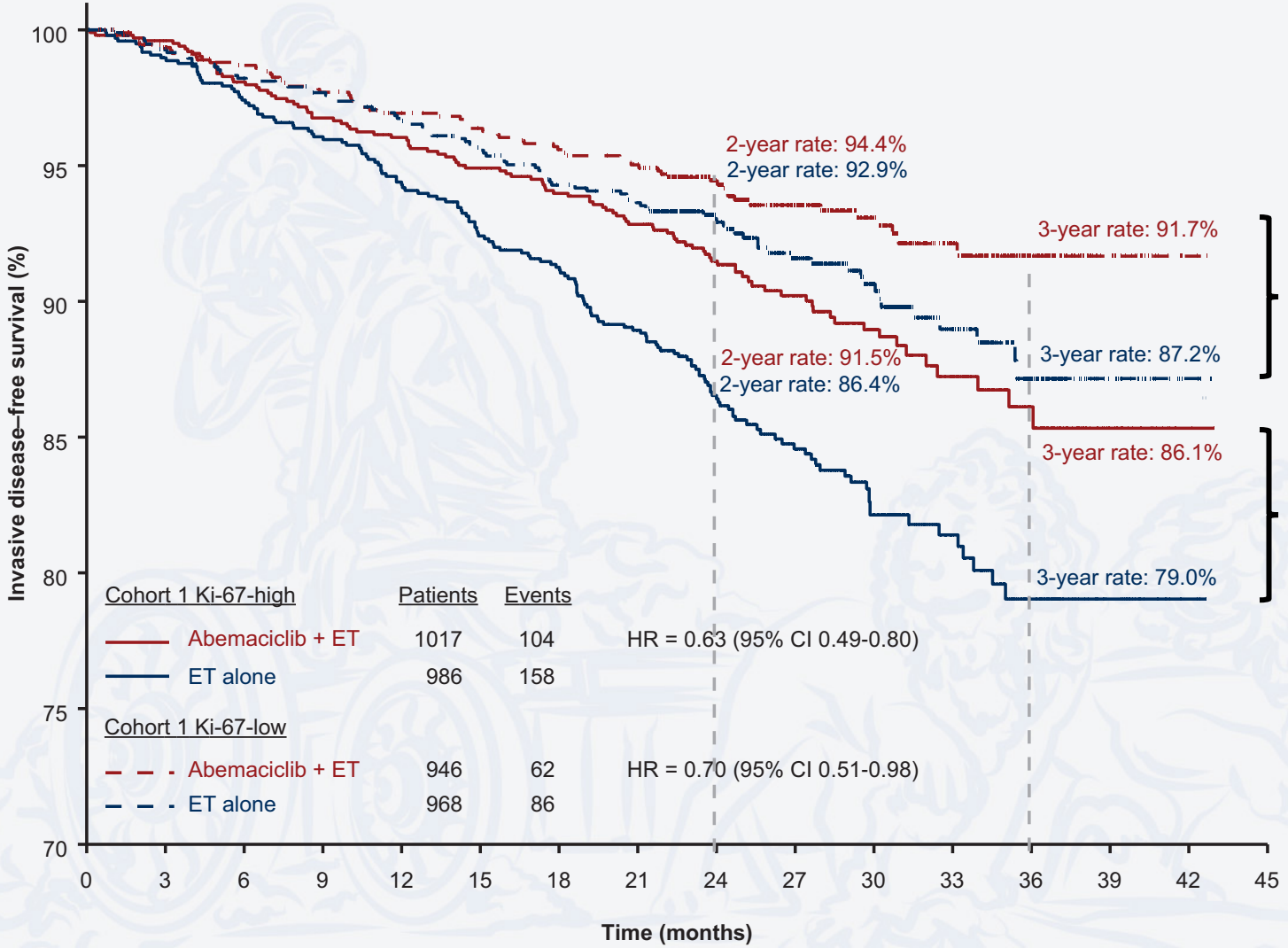
Secondary Objectives

- IDFS Ki 67 ≥20%
- IDFS Ki 67 ≥20%

Harbeck N, Ann Oncol 2021

IDFS in Cohort 1 Ki-67 high versus Ki-67 low

Exploratory Objectives



4,5% HR 0.7

7,1% HR 0.63

IDFS Ki 67<20%

IDFS Ki 67 ≥20%

Ki-67 is prognostic but does not predict benefit for abemaciclib

Harbeck N, Ann Oncol 2021

OS Interim Analysis (ITT population, Ki67 ≥20% populations)

Efficacy Parameter	ITT		Ki-67 ≥ 20% (cohort 1 + 2)		FDA-Approved Population: Ki-67 ≥ 20% (cohort 1)	
	Abemaciclib + ET (n = 2,808)	ET (n = 2,829)	Abemaciclib + ET (n = 1,262)	ET (n = 1,236)	Abemaciclib + ET (n = 1,017)	ET (n = 986)
IDFS events, No. (%)	232 (8)	333 (12)	118 (9)	172 (14)	104 (10)	158 (16)
HR (95% CI)	0.696 (0.588 to 0.823)		0.663 (0.524 to 0.839)		0.626 (0.488 to 0.803)	
P	< .0001[b]		.0006[b]		.0002[b]	
OS events, No. (%)	96 (3)	90 (3)	48 (4)	55 (4)	42 (4)	53 (5)
HR (95% CI)	1.091 (0.818 to 1.455)		0.851 (0.577 to 1.255)		0.767 (0.511 to 1.152)	

The immature OS analysis showed a nonsignificant HR > 1 showing a **potential detriment with abemaciclib plus ET in the ITT population.**

The point estimate numerically favors the abemaciclib plus ET arm (HR 0.767; 95% CI, 0.511 to 1.512) and **do not indicate a detrimental effect of treatment with adjuvant abemaciclib plus ET.**

Royce M, J Clin Oncol 2022

FDA approves abemaciclib with endocrine therapy for early breast cancer

On October 12,2021, the Food and Drug Administration approved abemaciclib (Verzenio,Eli Lilly and Company)with endocrine therapy (tamoxifen or an aromatase inhibitor) for **adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test**. This is the first CDK 4/6 inhibitor approved for adjuvant treatment of breast cancer.

FDA also approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay, submitted by Agilent, Inc., as a **companion diagnostic** for selecting patients for this indication.

monarchE: Conclusions

- **Abemaciclib + adjuvant ET** demonstrated clinically meaningful **improvement in IDFS & DRFS** in HR+/HER2- eBC

- Benefit is maintaned beyond 2-year treatment period
- Safety was consistent with profile of abemaciclib
- Ki-67 index was prognostic

Why PALLAS and monarchE were different?

- **Different Risk of Recurrence**
- **Different Discontinuation rate**
- **Different mechanism of action**
  - Kinase inhibitory activity
  - Effect on cell-cycle
  - Schedule

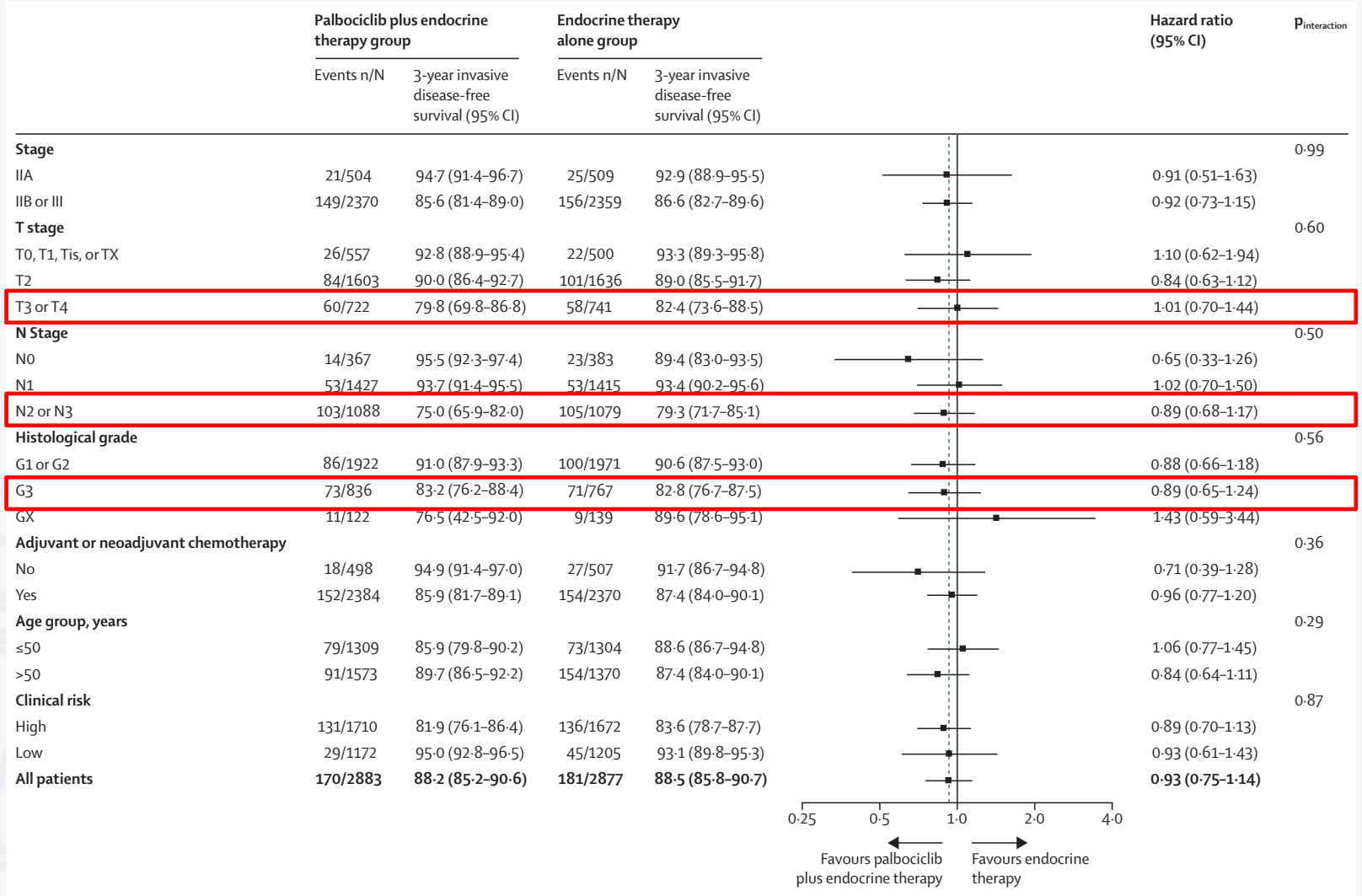
XXIV Simposio de Revisiones en Cáncer
"Tratamiento médico del cáncer en el año 2022"

Different Risks of Recurrence

	PALLAS	MONARCH-E
T≥3	25%	21.6%
≥ 4 nodes	37.8%	59.9%
Grade 3	29%	38.7%
Ki 67 ≥ 20	N/A	44.9%

58.7% had high clinical risk disease in PALLAS trial:

- **≥4 nodes involved (≥N2) or**
- **1-3 nodes with either T3-T4 and/or G3 disease**



	Palbociclib plus endocrine therapy group		Endocrine therapy alone group		Hazard ratio (95% CI)	$p_{interaction}$
	Events n/N	3-year invasive disease-free survival (95% CI)	Events n/N	3-year invasive disease-free survival (95% CI)		
Stage						0·99
IIA	21/504	94·7 (91·4–96·7)	25/509	92·9 (88·9–95·5)	0·91 (0·51–1·63)	
IIB or III	149/2370	85·6 (81·4–89·0)	156/2359	86·6 (82·7–89·6)	0·92 (0·73–1·15)	
T stage						0·60
T0, T1, Tis, or TX	26/557	92·8 (88·9–95·4)	22/500	93·3 (89·3–95·8)	1·10 (0·62–1·94)	
T2	84/1603	90·0 (86·4–92·7)	101/1636	89·0 (85·5–91·7)	0·84 (0·63–1·12)	
T3 or T4	60/722	79·8 (69·8–86·8)	58/741	82·4 (73·6–88·5)	1·01 (0·70–1·44)	
N Stage						0·50
N0	14/367	95·5 (92·3–97·4)	23/383	89·4 (83·0–93·5)	0·65 (0·33–1·26)	
N1	53/1427	93·7 (91·4–95·5)	53/1415	93·4 (90·2–95·6)	1·02 (0·70–1·50)	
N2 or N3	103/1088	75·0 (65·9–82·0)	105/1079	79·3 (71·7–85·1)	0·89 (0·68–1·17)	
Histological grade						0·56
G1 or G2	86/1922	91·0 (87·9–93·3)	100/1971	90·6 (87·5–93·0)	0·88 (0·66–1·18)	
G3	73/836	83·2 (76·2–88·4)	71/767	82·8 (76·7–87·5)	0·89 (0·65–1·24)	
GX	11/122	76·5 (42·5–92·0)	9/139	89·6 (78·6–95·1)	1·43 (0·59–3·44)	
Adjuvant or neoadjuvant chemotherapy						0·36
No	18/498	94·9 (91·4–97·0)	27/507	91·7 (86·7–94·8)	0·71 (0·39–1·28)	
Yes	152/2384	85·9 (81·7–89·1)	154/2370	87·4 (84·0–90·1)	0·96 (0·77–1·20)	
Age group, years						0·29
≤50	79/1309	85·9 (79·8–90·2)	73/1304	88·6 (86·7–94·8)	1·06 (0·77–1·45)	
>50	91/1573	89·7 (86·5–92·2)	154/1370	87·4 (84·0–90·1)	0·84 (0·64–1·11)	
Clinical risk						0·87
High	131/1710	81·9 (76·1–86·4)	136/1672	83·6 (78·7–87·7)	0·89 (0·70–1·13)	
Low	29/1172	95·0 (92·8–96·5)	45/1205	93·1 (89·8–95·3)	0·93 (0·61–1·43)	
All patients	**170/2883**	**88·2 (85·2–90·6)**	**181/2877**	**88·5 (85·8–90·7)**	**0·93 (0·75–1·14)**	

Johnston S. ESMO 2020,Mayer EL, Lancet Oncol 2021

Different Discontinuation Rate

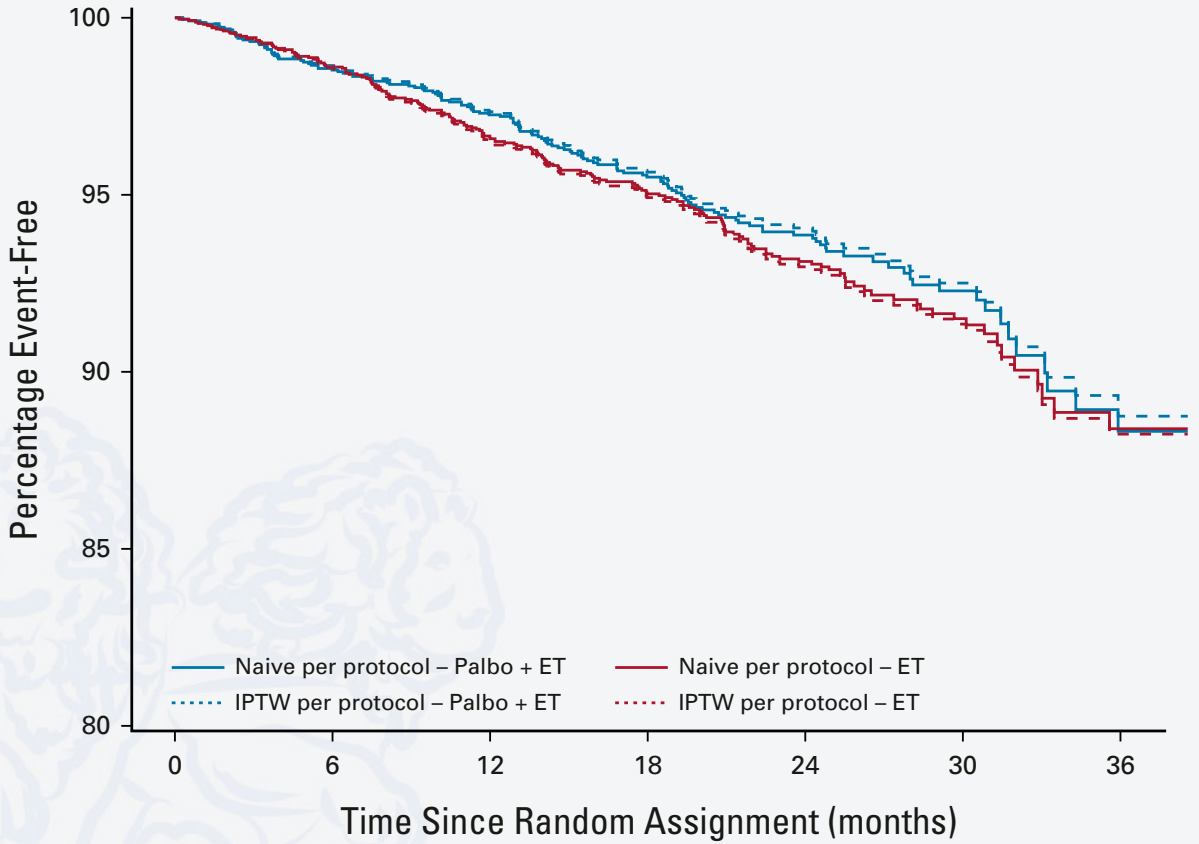
PALLAS Trial

42.2% treatment discontinuation

Monarch-E

16% treatment discontinuation

iDFS in palbociclib + ET versus ET alone in adherent patients



No. at risk:

Naive – Palbo + ET	2,237	2,193	2,130	1,614	1,040	472	134
Naive – ET	2,799	2,606	2,498	1,926	1,261	568	169
IPTW – Palbo + ET	2,237	2,195	2,132	1,619	1,045	474	136
IPTW – ET	2,798	2,603	2,494	1,918	1,252	563	166

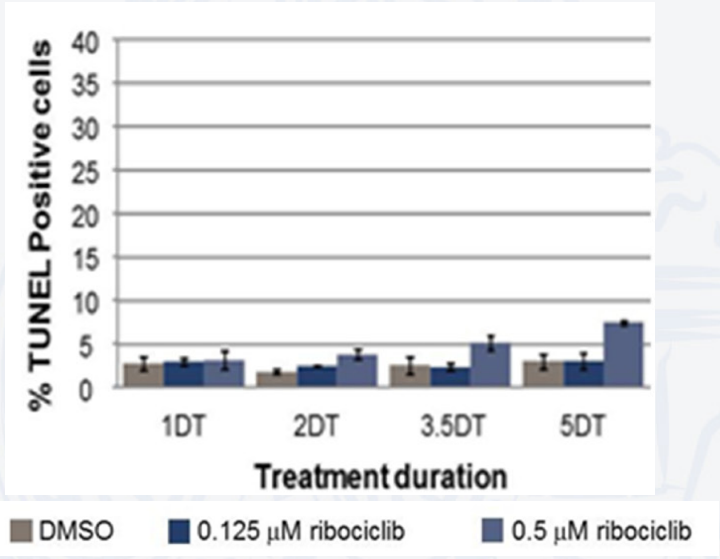
Mayer EL, J Clin Oncol 2022; Harbeck N, Ann Oncol 2021

Different mechanisms of action

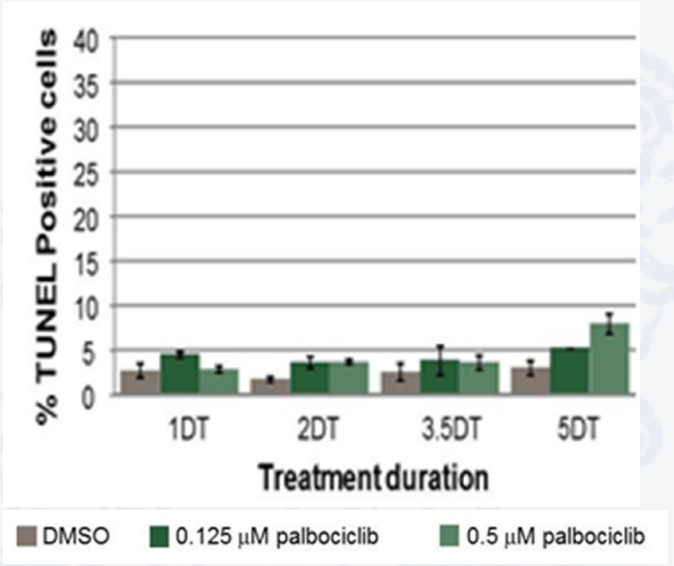
- **Abemaciclib studies report high IC50s: 2 nM for CDK4 and 10 nM for CDK6.**
- **Continuous inhibition yields cell arrest**
- **Induction of senescence and apoptosis**

Fragmentation of DNA ends and sencescene assesed using TUNEL staining

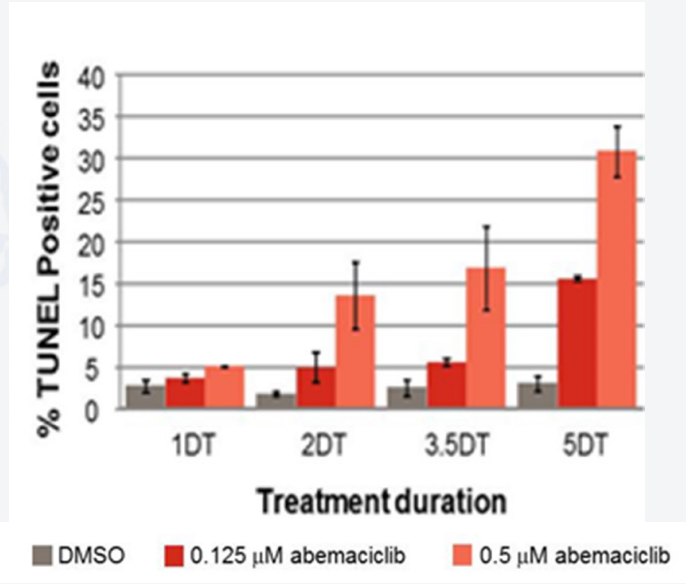
Ribociclib



Palbociclib



Abemaciclib

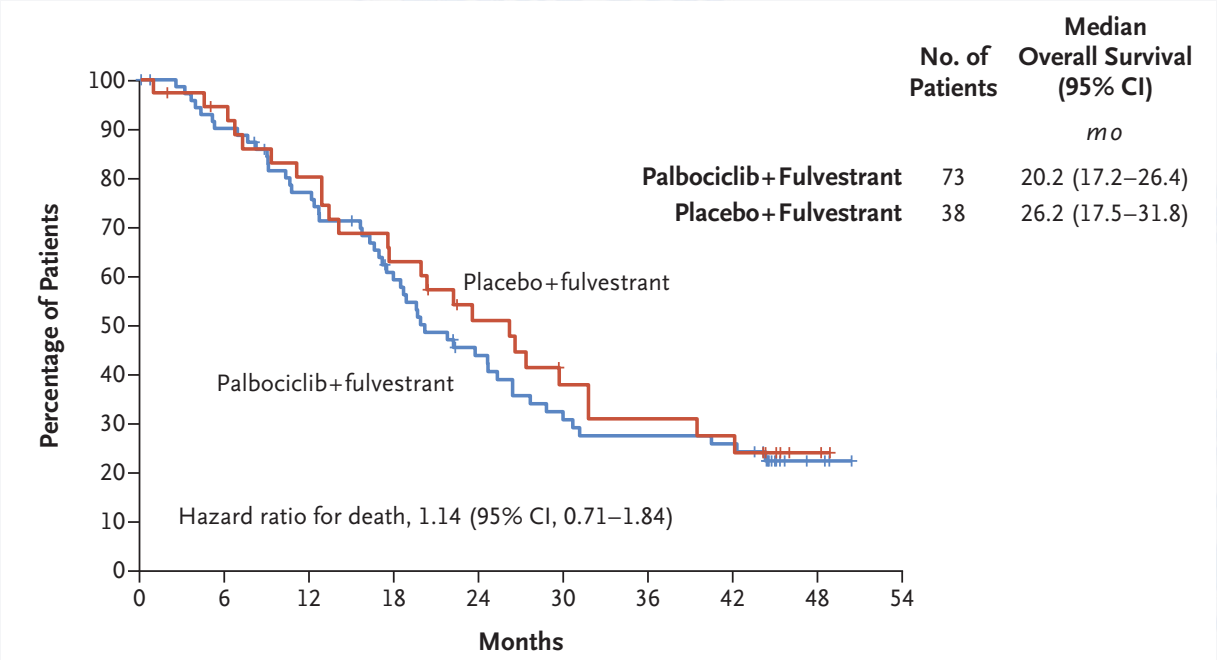


Gelbert LM, Investigational New Drugs 2014;Tate SC, Clinical Cancer Research 2014; Torres-Guzmán R, Oncotarget 2017

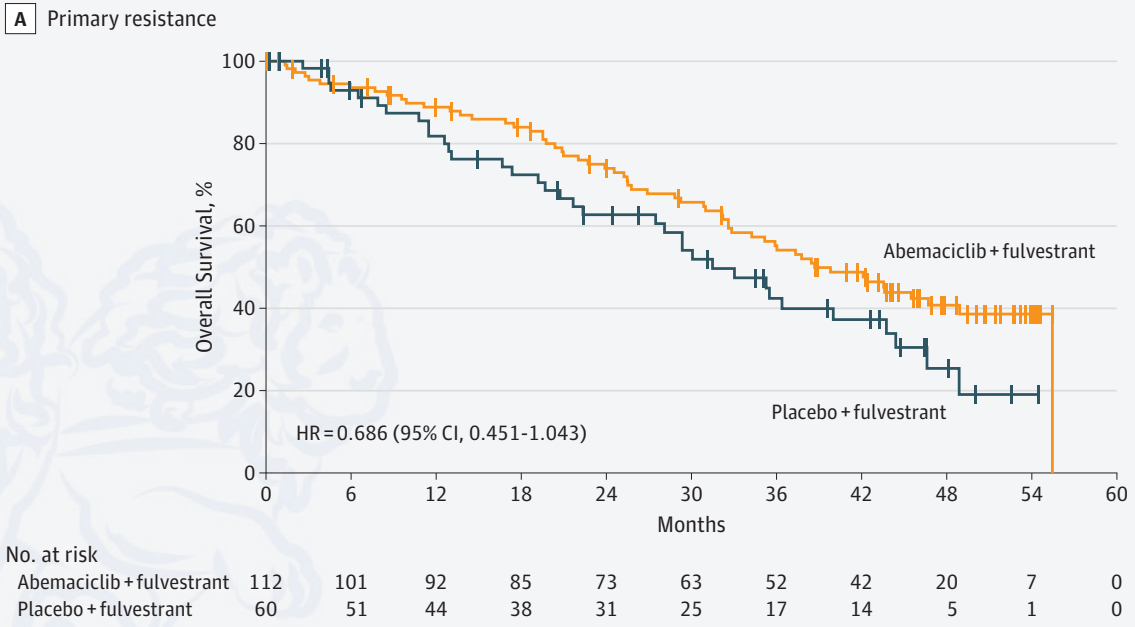
Different mechanisms of action

iCDKs + Fulvestrant in Endocrine Resistant ER+ HER2 – Breast Cancer

PALOMA 3: OS in patients without sensitivity to previous endocrine therapy



MONARCH 2: OS in patients with primary endocrine resistance



Turner N, NEJM 2015, Sledge RW, JCO 2017

Unanswered questions about iCDKs in EBC

- Who needs adjuvant iCDK 4/6 therapy?
  - Better biomarkers apart from stage
- What is the long-term impact from the adjuvant use of iCDK4/6?
  - Abemaciclib prevents early recurrences (Endocrine resistant disease)
  - Effect in late recurrences (endocrine sensitive) and OS is unknown
  - Longer follow-up is needed
- What is the optimal duration of adjuvant iCDKs?
- Is there any benefit in intermediate risk tumors?
- Role of iCDKs in neoadjuvant setting
- Compliance and safety in real world practice