New Therapeutic Approaches for Hormone Receptor-Positive Early Breast Cancer

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Celebrating Women Chair in Breast Cancer

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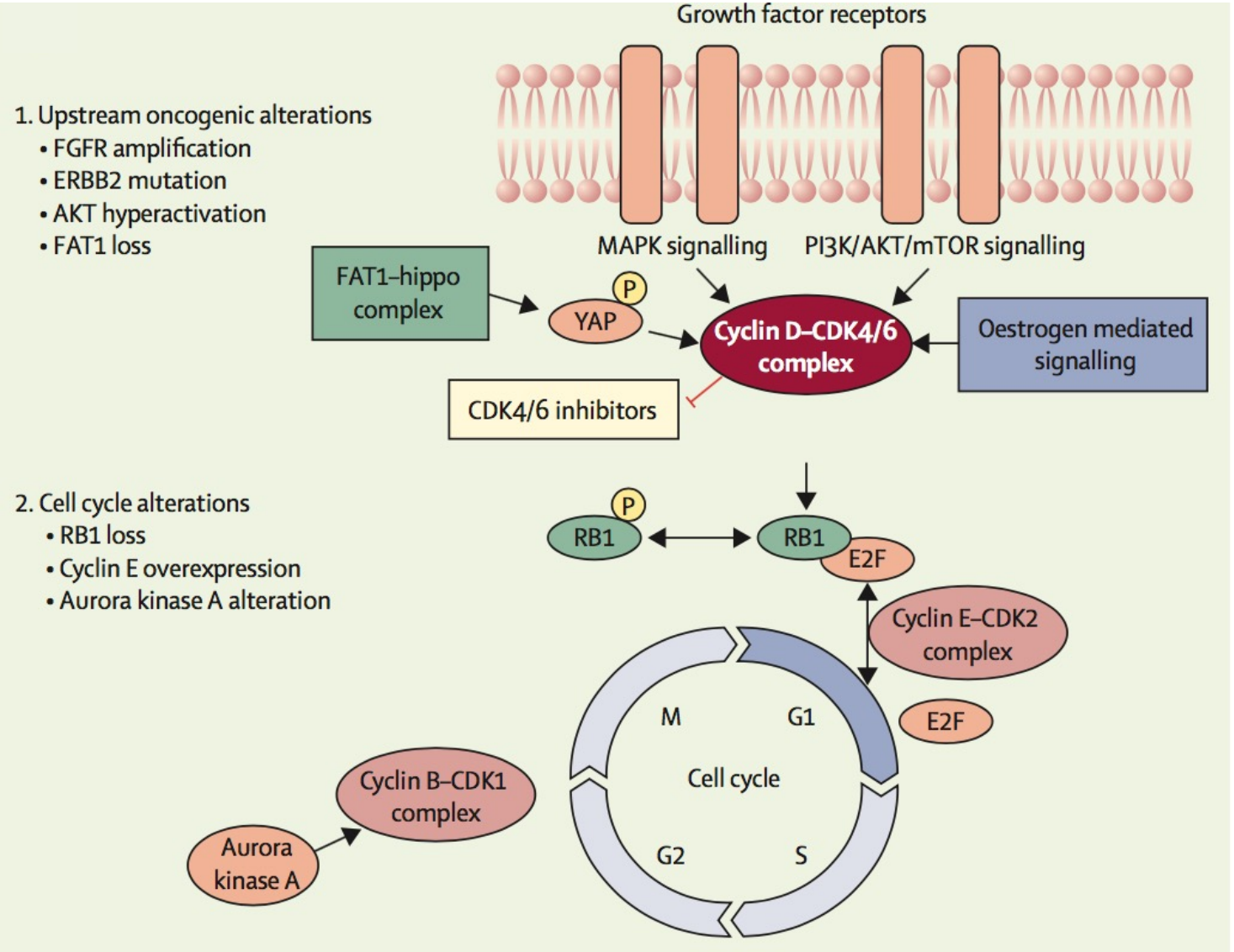
Texas Oncology

US Oncology

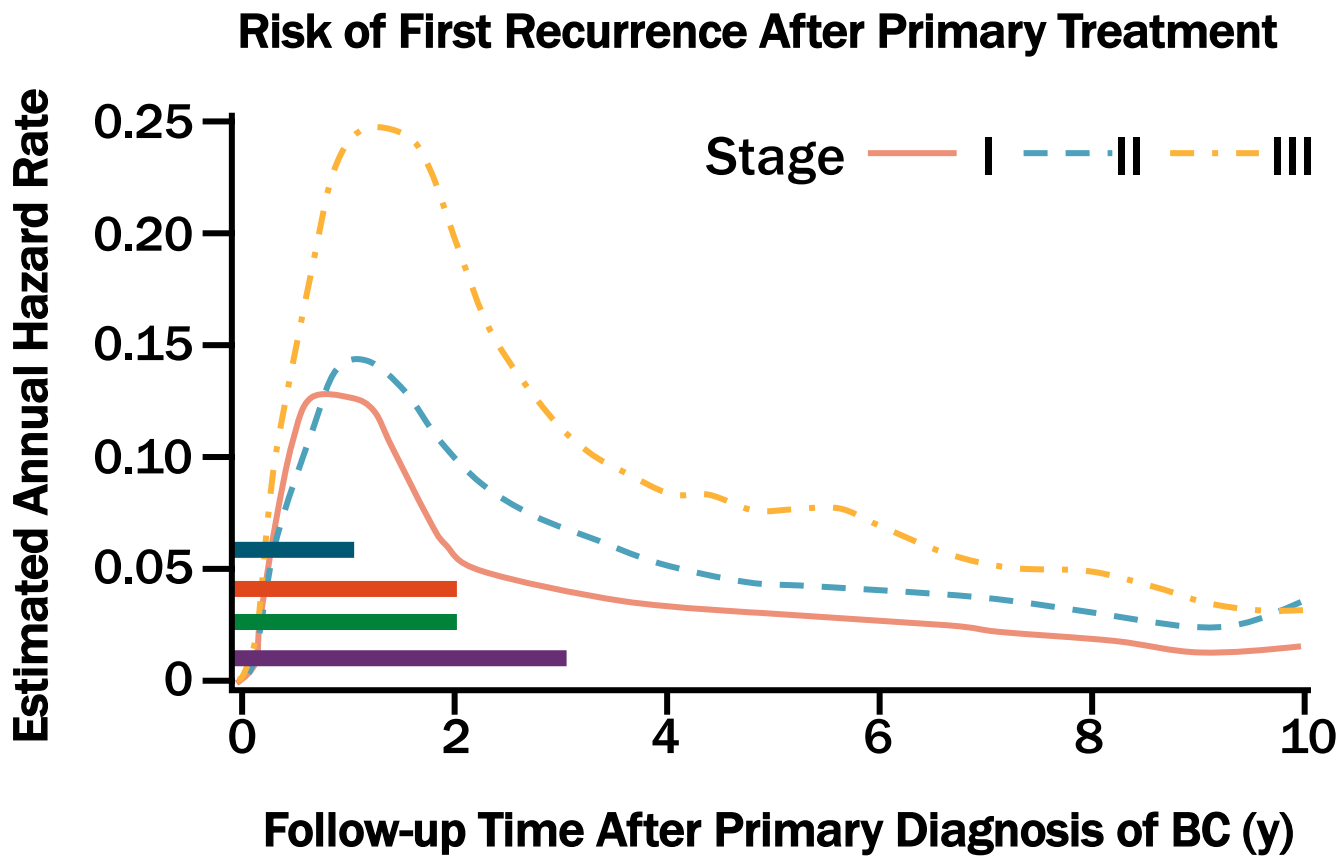
Mechanisms of Action of CDK4/6 Inhibitors



	Palbociclib	Ribociclib	Abemaciclib
IC_{50} (nM)			
Cyclin D1–CDK4	11	10	2
Cyclin D1/2/3–CDK6	16	39	10
Cyclin B–CDK1	>10 000	113 000	1627
Cyclin A/E–CDK2	>10 000	76 000	504
Cyclin T–CDK9	NR	NR	57
Mean terminal half-life (h)	26	36	17–38
Standard dosing	125 mg daily (3 weeks on, 1 week off)	600 mg daily 3 weeks on, 1 week off)	150 mg twice daily in combination with antioestrogen; 200 mg twice daily as monotherapy

Reprinted from The Lancet, 395, Spring LM, et al. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. 817–27, 2020, with permission from Elsevier.

Is There a Role for CDK4/6 Inhibition for Early-Stage HR+ Disease?



PENELOPE-B
palbociclib
After neoadjuvant, high risk

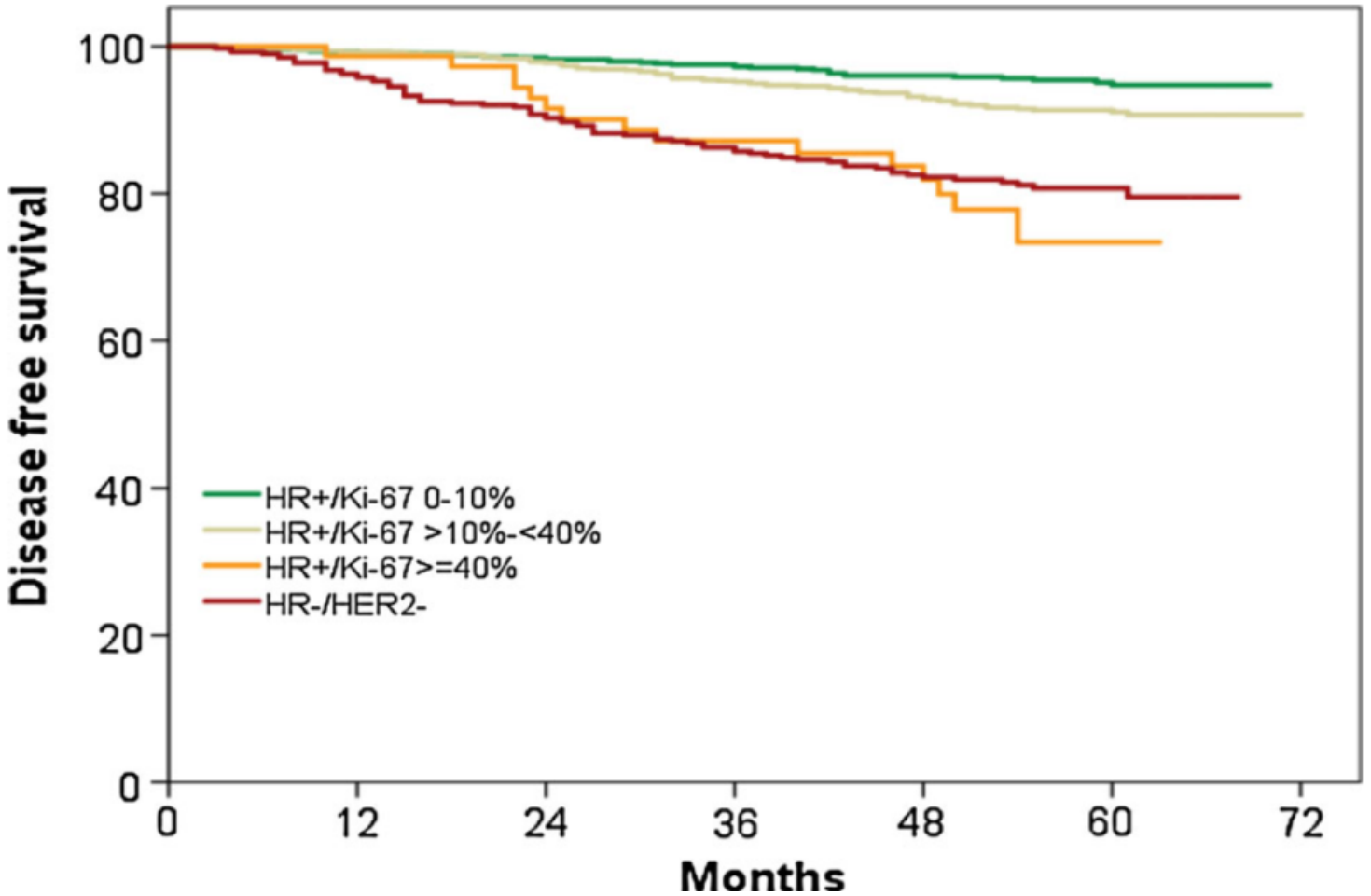
monarchE
abemaciclib
High-risk anatomic factors, Ki67

PALLAS
palbociclib
Stage II, III

NATALEE
ribociclib
Stage II, III

Cheng L, et al. Cancer Epidemiol Biomarkers Prev. 2012;21:800-809.

WSG PlanB Trial in Luminal B Early Breast Cancer
Tumor Biology and Ki-67 Impact Survival



Luminal A

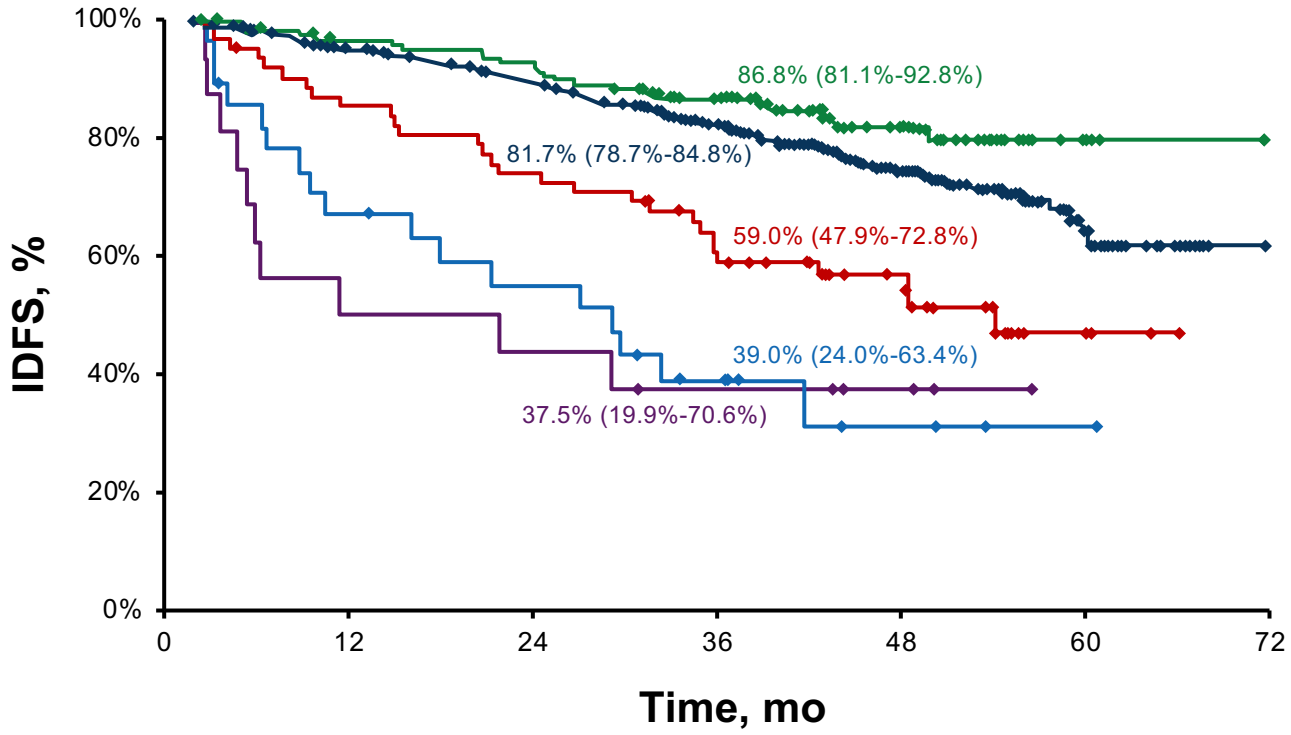
Luminal B (intermediate proliferation)

Triple Negative

Luminal B (high proliferation)

Nitz U, et al. *Breast Cancer Res Treat*. 2017;165:573-583.

PENELOPE-B: IDFS by Intrinsic Molecular Subtyping: LumB with high Ki-67



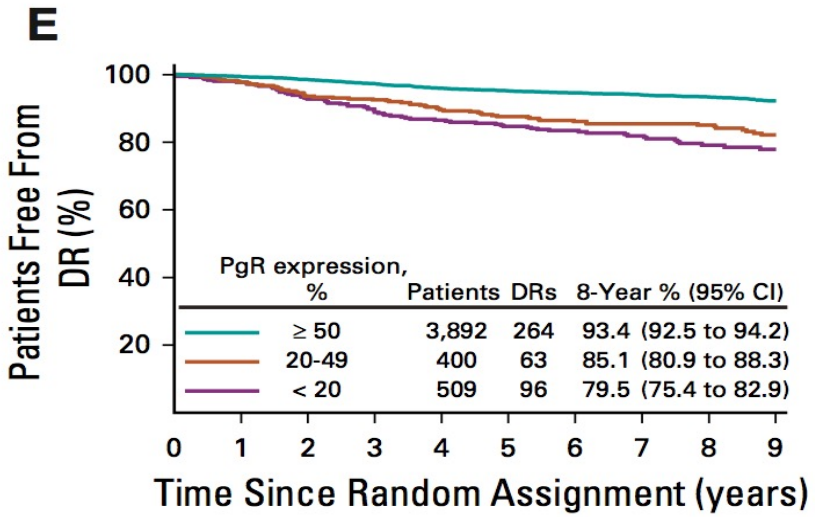
LumA	663	604	555	405	176	32	1
LumB	64	53	45	33	19	3	0
NormL	135	125	117	93	45	6	0
BasalL	16	8	7	5	3	0	0
HER2E	28	17	14	6	3	1	0

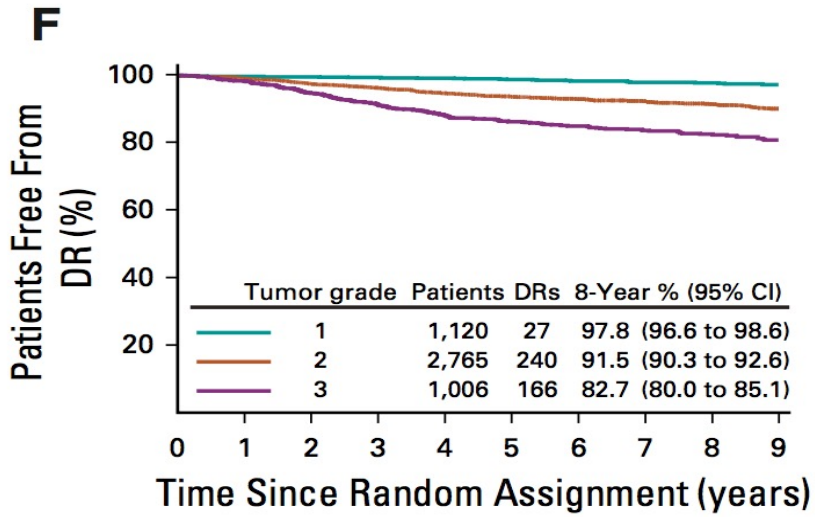
Gene expression data (906 of 1,250 [72%] patients)

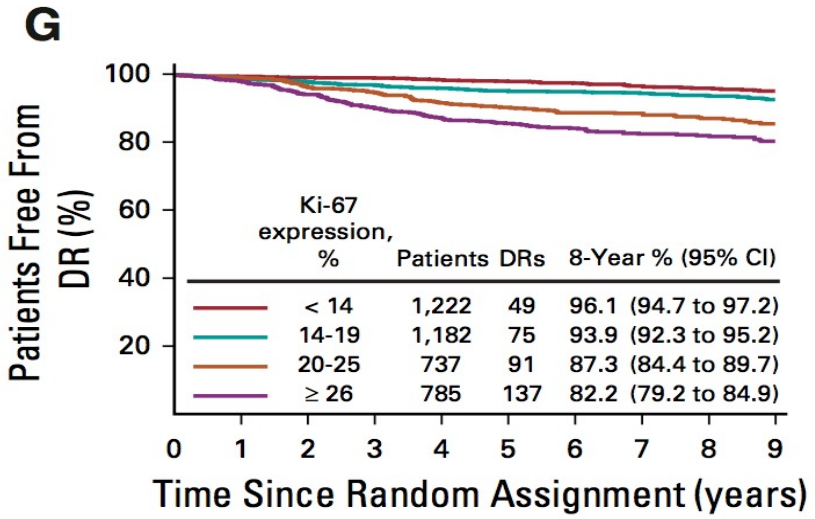
- 663 LumA
- 64 LumB
- 135 NormL
- 16 BasalL and 28 HER2E

1. Denkert C et al. ASCO 2021. Abstract 519.

Prognostic Factors for Premenopausal ER+ Pts: SOFT and TEXT Trials: High Ki-67

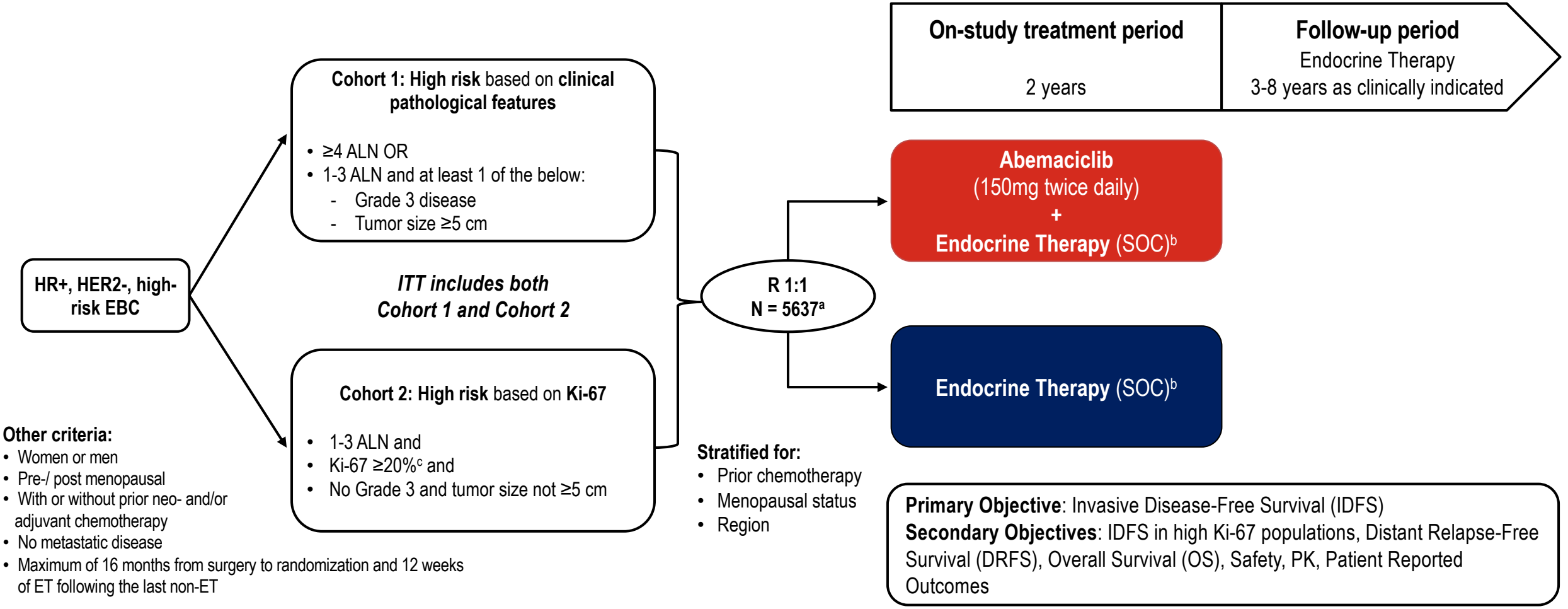






Pagani O, et al. J Clin Oncol. 2020;38:1293-1303.

monarchE Study Design (NCT03155997)



[a]Recruitment from July 2017 to August 2019; [b]Endocrine therapy of physician's choice [e.g. aromatase inhibitors, tamoxifen, LHRH agonist]; [c]Ki-67 expression centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent

Abbreviations: ALN = positive axillary lymph nodes; CPF = clinicopathological features; HER2 = human epidermal receptor 2; HR = hormone receptor; ITT = intent-to-treat population; N = number of patients in the ITT population; R = randomized; SOC = standard of care

Baseline Characteristics of ITT

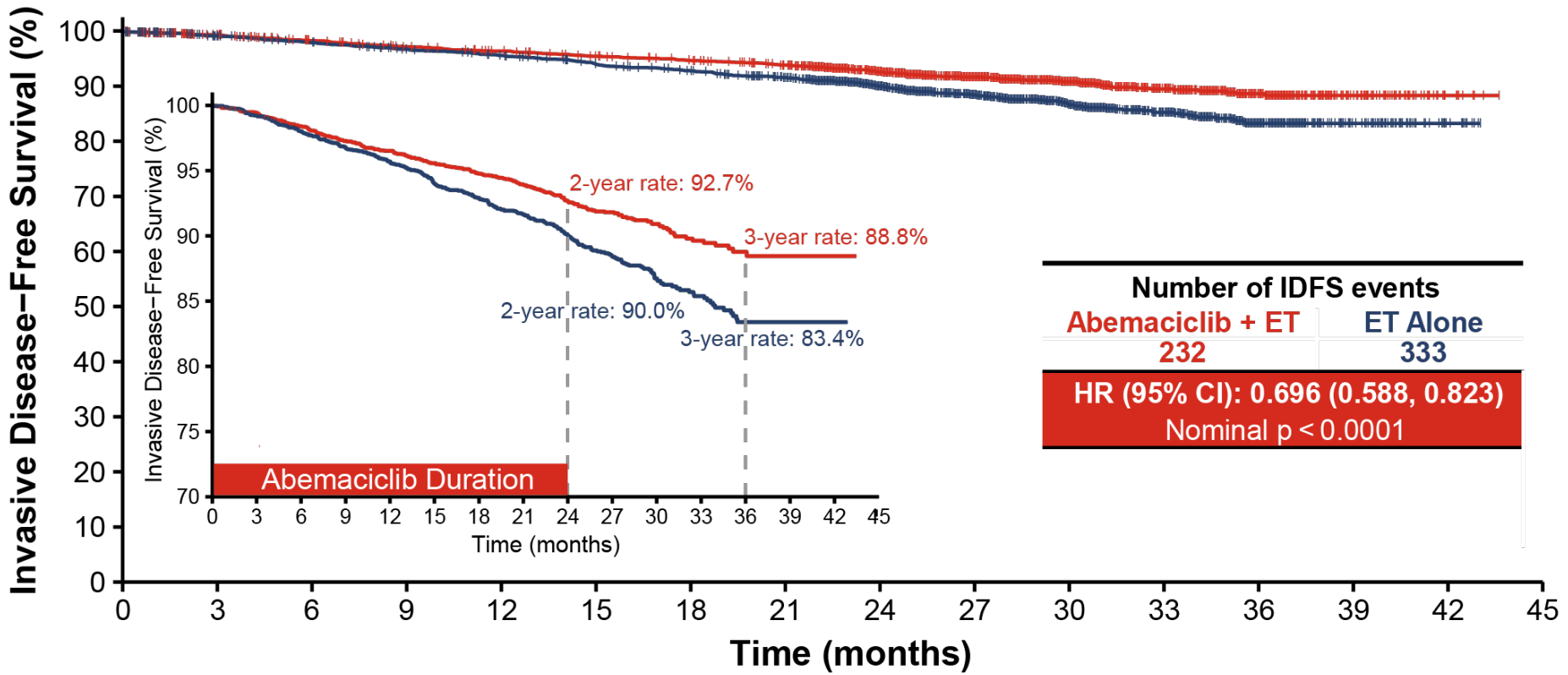
		Abemaciclib + ET N=2808, %	ET Alone N=2829, %
Age	Median (range)	51 (23-89)	51 (22-86)
Age categories	<65 years	84.4	85.4
Gender	Female	99.3	99.5
Menopausal Status[1]	Premenopausal	43.5	43.5
	Postmenopausal	56.5	56.5
Prior Chemotherapy[1]	Neoadjuvant	37.0	37.0
	Adjuvant	58.5	58.2
	None	4.5	4.7
Baseline 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

Note: data generated at Primary Outcome analysis (July 2020); where values do not add up to 100%, remaining data are missing, unavailable, or could not be assessed

[1]Per Interactive Web Response System (IWRS)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = Endocrine Therapy

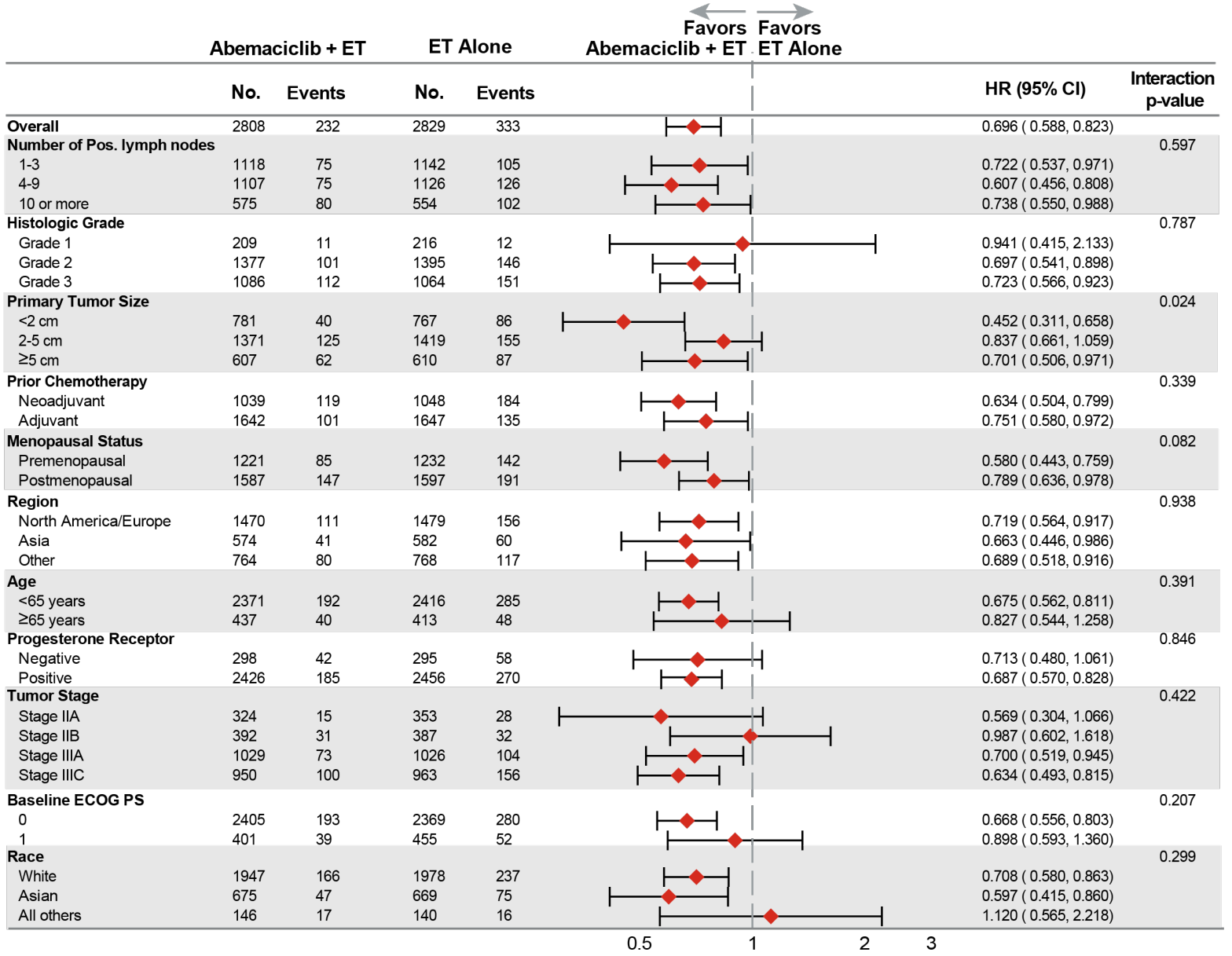
IDFS Benefit Maintained with Additional Follow-up in ITT population



Number at risk																
Abemaciclib + ET	2808	2680	2621	2579	2547	2508	2477	2430	1970	1287	919	522	275	67	8	0
ET Alone	2829	2700	2652	2608	2572	2513	2472	2400	1930	1261	906	528	281	64	10	0

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.

Consistent IDFS Treatment Benefit Observed in Prespecified Subgroups



	Abemaciclib + ET		ET Alone		HR (95% CI)	Interaction p-value
	No.	Events	No.	Events		
Overall	2808	232	2829	333	0.696 (0.588, 0.823)	
Number of Pos. lymph nodes						0.597
1-3	1118	75	1142	105	0.722 (0.537, 0.971)	
4-9	1107	75	1126	126	0.607 (0.456, 0.808)	
10 or more	575	80	554	102	0.738 (0.550, 0.988)	
Histologic Grade						0.787
Grade 1	209	11	216	12	0.941 (0.415, 2.133)	
Grade 2	1377	101	1395	146	0.697 (0.541, 0.898)	
Grade 3	1086	112	1064	151	0.723 (0.566, 0.923)	
Primary Tumor Size						0.024
<2 cm	781	40	767	86	0.452 (0.311, 0.658)	
2-5 cm	1371	125	1419	155	0.837 (0.661, 1.059)	
≥5 cm	607	62	610	87	0.701 (0.506, 0.971)	
Prior Chemotherapy						0.339
Neoadjuvant	1039	119	1048	184	0.634 (0.504, 0.799)	
Adjuvant	1642	101	1647	135	0.751 (0.580, 0.972)	
Menopausal Status						0.082
Premenopausal	1221	85	1232	142	0.580 (0.443, 0.759)	
Postmenopausal	1587	147	1597	191	0.789 (0.636, 0.978)	
Region						0.938
North America/Europe	1470	111	1479	156	0.719 (0.564, 0.917)	
Asia	574	41	582	60	0.663 (0.446, 0.986)	
Other	764	80	768	117	0.689 (0.518, 0.916)	
Age						0.391
<65 years	2371	192	2416	285	0.675 (0.562, 0.811)	
≥65 years	437	40	413	48	0.827 (0.544, 1.258)	
Progesterone Receptor						0.846
Negative	298	42	295	58	0.713 (0.480, 1.061)	
Positive	2426	185	2456	270	0.687 (0.570, 0.828)	
Tumor Stage						0.422
Stage IIA	324	15	353	28	0.569 (0.304, 1.066)	
Stage IIB	392	31	387	32	0.987 (0.602, 1.618)	
Stage IIIA	1029	73	1026	104	0.700 (0.519, 0.945)	
Stage IIIC	950	100	963	156	0.634 (0.493, 0.815)	
Baseline ECOG PS						0.207
0	2405	193	2369	280	0.668 (0.556, 0.803)	
1	401	39	455	52	0.898 (0.593, 1.360)	
Race						0.299
White	1947	166	1978	237	0.708 (0.580, 0.863)	
Asian	675	47	669	75	0.597 (0.415, 0.860)	
All others	146	17	140	16	1.120 (0.565, 2.218)	

Abemaciclib Treatment Effect Over Time

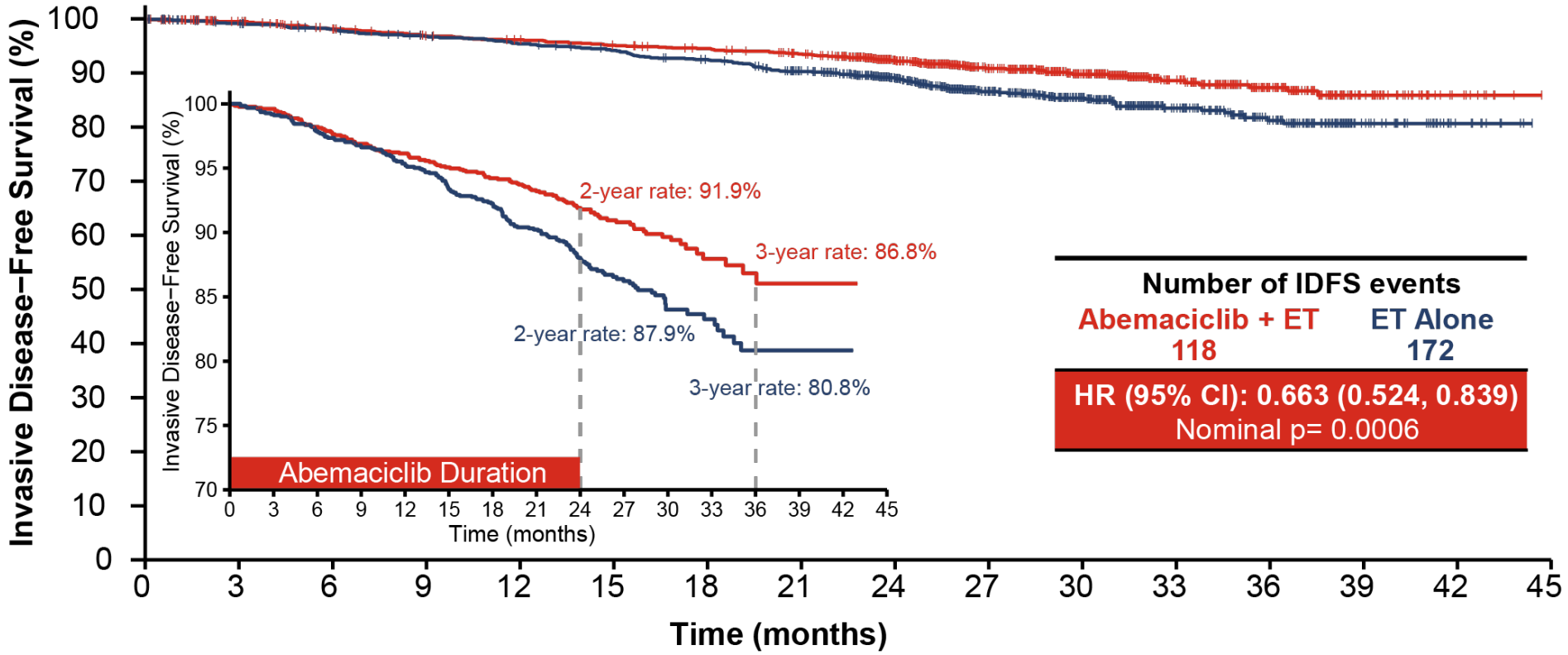
monarchE
EARLY BREAST CANCER

Analysis landmark	IDFS			DRFS		
	Events		Piecewise HR* (95% CI**)	Events		Piecewise HR* (95% CI**)
	Abemaciclib + ET	ET Alone		Abemaciclib + ET	ET Alone	
Year 0-1	93	116	0.795 (0.589, 1.033)	67	91	0.732 (0.520, 0.987)
Year 1-2	98	146	0.681 (0.523, 0.869)	85	129	0.675 (0.507, 0.875)
Year 2+	41	71	0.596 (0.397, 0.855)	39	58	0.692 (0.448, 1.032)

* Piecewise hazard ratio was estimated using piecewise exponential model to assess the yearly treatment effect size
** 95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

Increasing magnitude of IDFS and DRFS effect size from the first year to the second year, with maintained treatment benefit beyond the 2-year study treatment period.

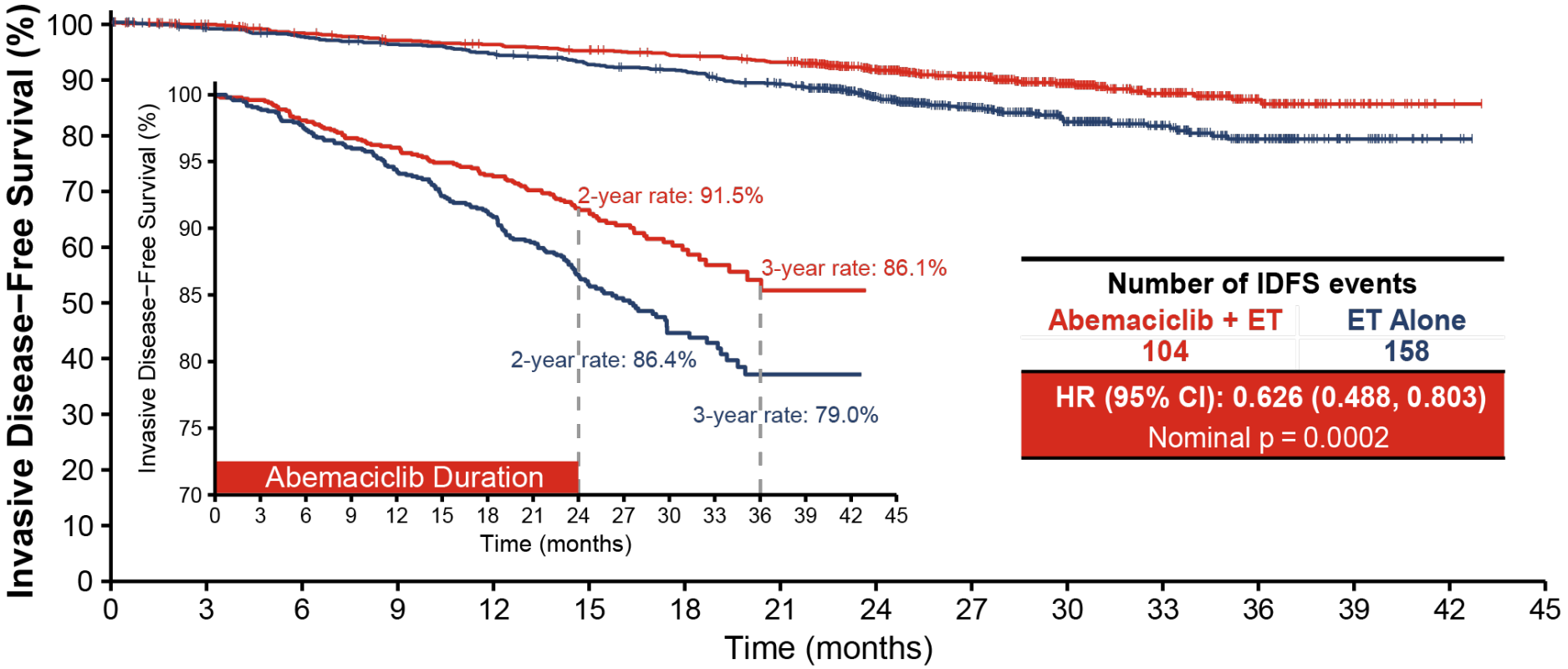
IDFS in ITT Ki-67 High (≥ 20%) Population



Number at risk																
Abemaciclib + ET	1262	1221	1189	1167	1155	1139	1123	1094	870	546	377	203	109	25	2	0
ET Alone	1236	1197	1177	1158	1142	1114	1096	1041	827	520	367	198	107	25	3	0

33.7% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 6.0% at 3 years.

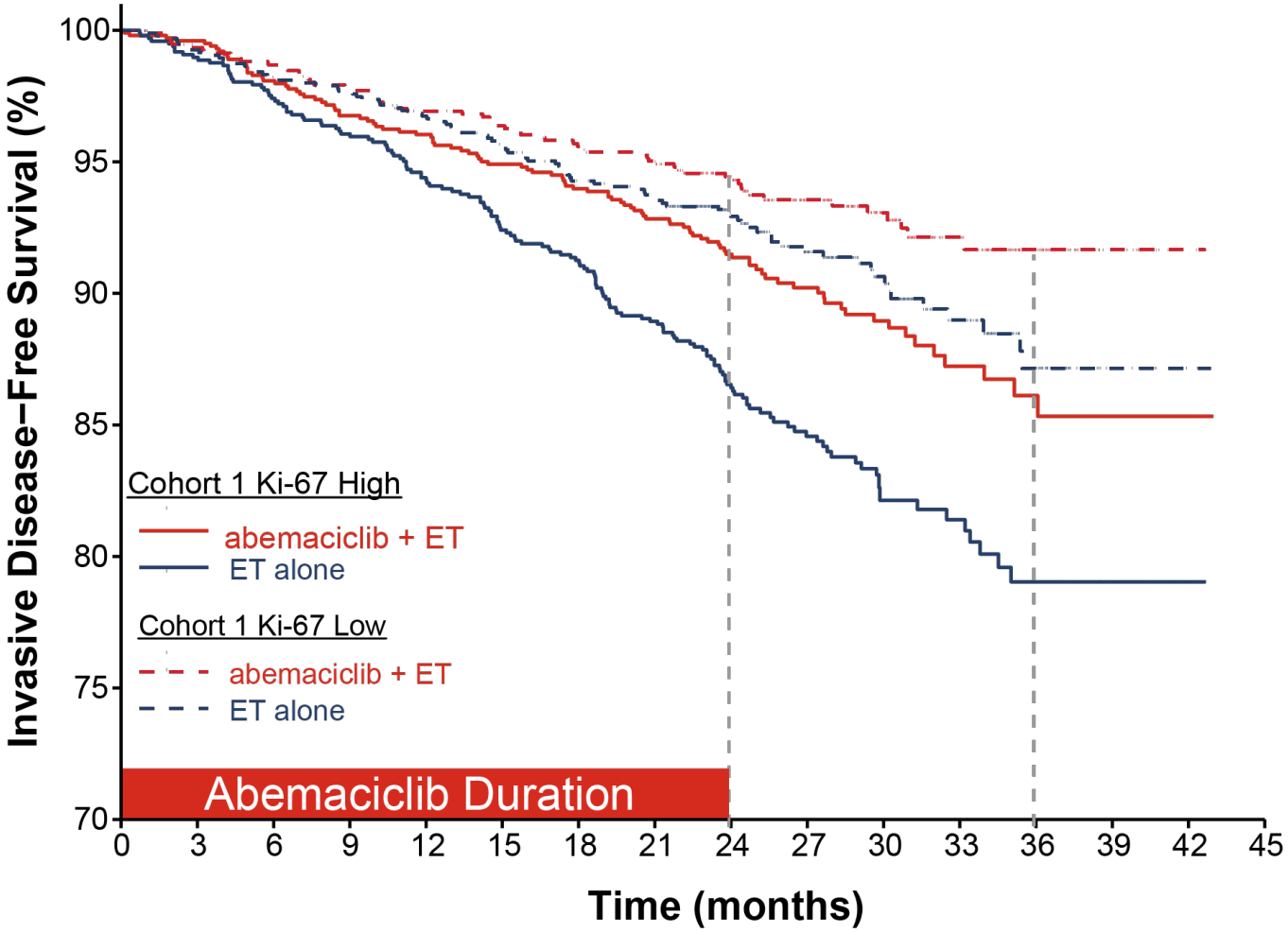
IDFS in Cohort 1 Ki-67 High (≥ 20%) Population



Number at risk																
Abemaciclib + ET	1017	989	963	946	936	922	908	894	733	484	348	203	109	25	2	0
ET Alone	986	955	938	922	906	883	868	835	687	457	333	197	107	25	3	0

37.4% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 7.1% at 3 years.

Ki-67 as a prognostic marker in Cohort 1



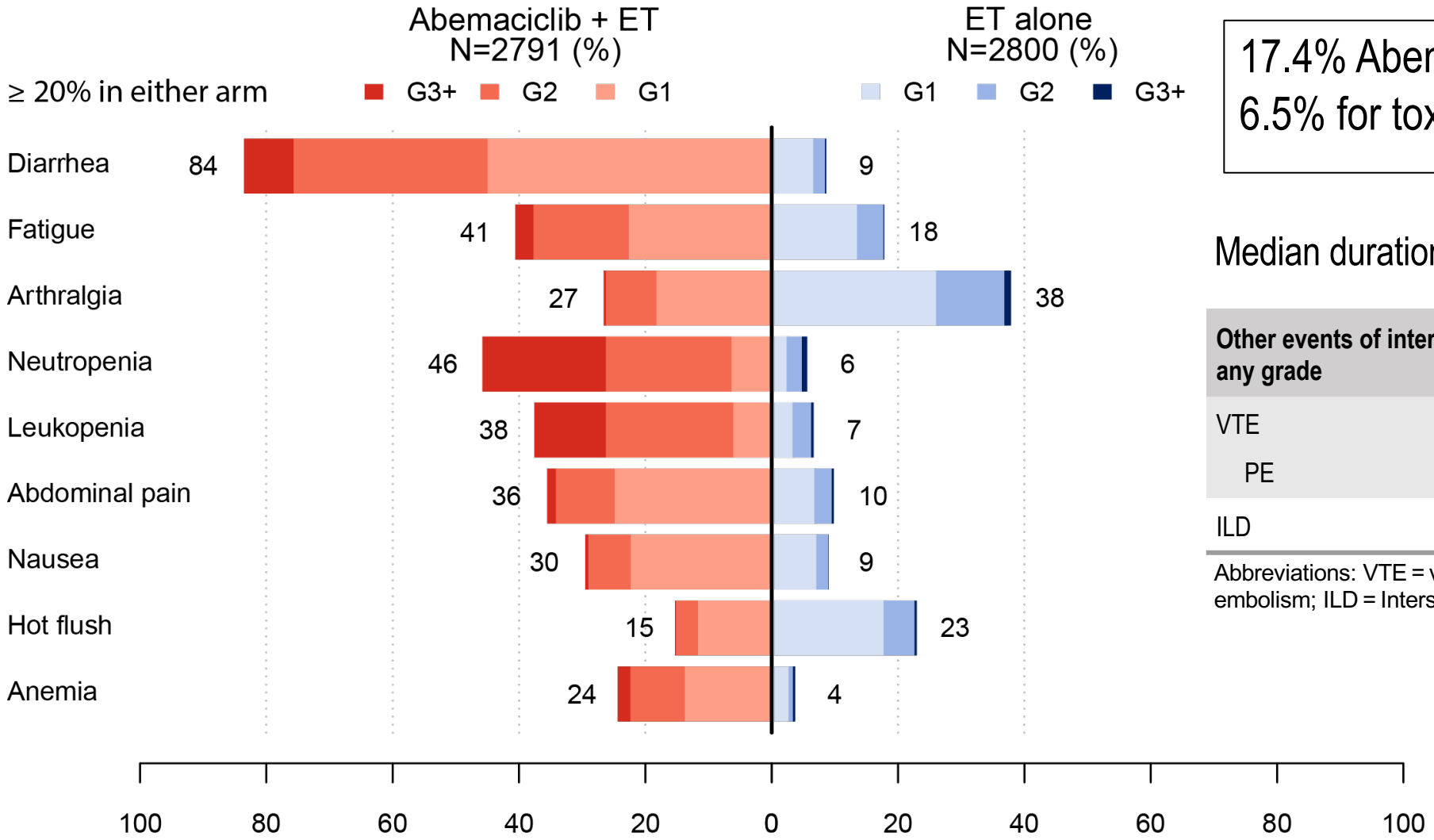
	Abemaciclib + ET	ET Alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

Ki-67 is prognostic

Ki-67 is not predictive of abemaciclib benefit

As expected, high Ki-67 index was prognostic of worse outcome.
However, abemaciclib benefit was consistent regardless of Ki-67 index.

Mature Safety Findings Consistent with Previous Analyses



All patients who received at least one dose of study treatment were included in the safety population

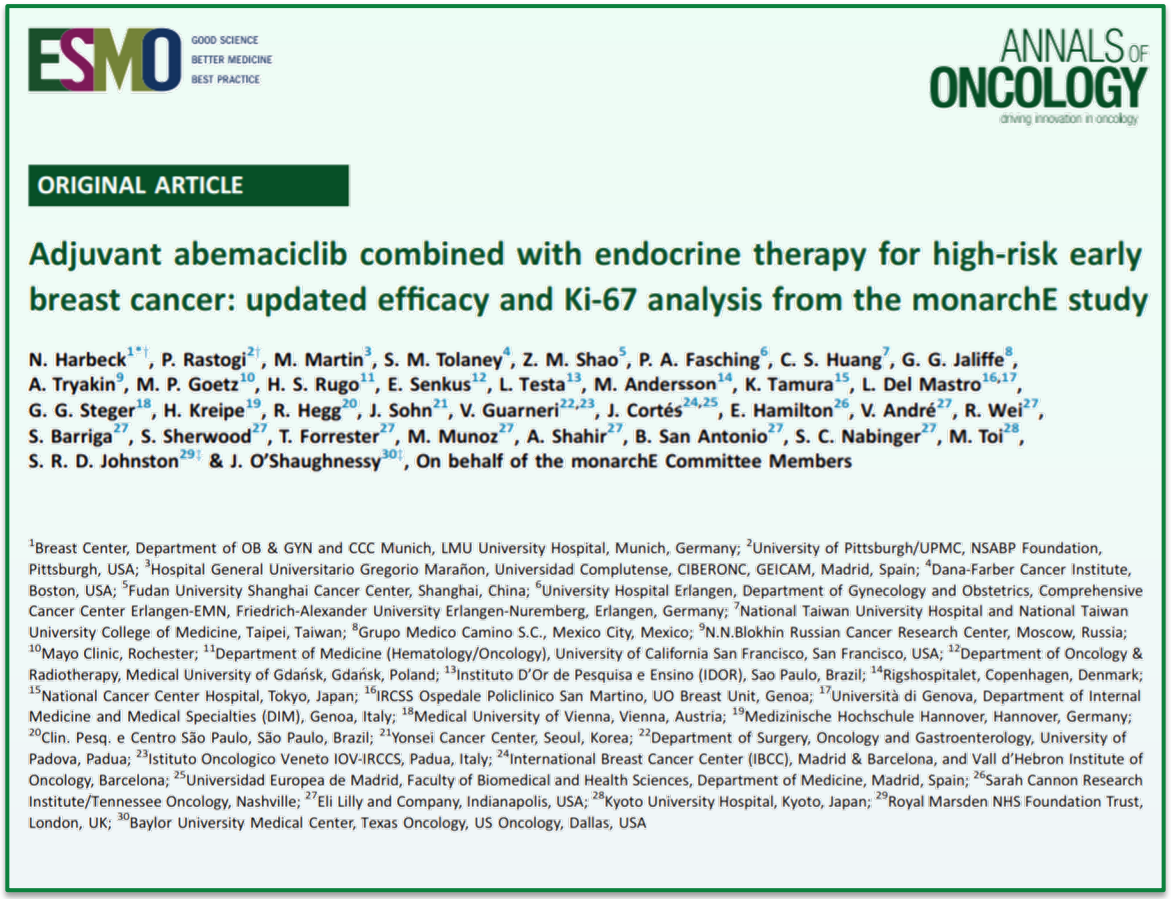
17.4% Abemaciclib discontinuation rate,
6.5% for toxicity

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

Adjuvant Abemaciclib for High-Risk, HR+/HER2-, Early Breast Cancer[1,2]



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study

N. Harbeck[1*†], P. Rastogi[2†], M. Martin[3], S. M. Tolaney[4], Z. M. Shao[5], P. A. Fasching[6], C. S. Huang[7], G. G. Jaliffe[8], A. Tryakin[9], M. P. Goetz[10], H. S. Rugo[11], E. Senkus[12], L. Testa[13], M. Andersson[14], K. Tamura[15], L. Del Mastro[16,17], G. G. Steger[18], H. Kreipe[19], R. Hegg[20], J. Sohn[21], V. Guarneri[22,23], J. Cortés[24,25], E. Hamilton[26], V. André[27], R. Wei[27], S. Barriga[27], S. Sherwood[27], T. Forrester[27], M. Munoz[27], A. Shahir[27], B. San Antonio[27], S. C. Nabinger[27], M. Toi[28], S. R. D. Johnston[29‡] & J. O'Shaughnessy[30‡], On behalf of the monarchE Committee Members

[1]Breast Center, Department of OB & GYN and CCC Munich, LMU University Hospital, Munich, Germany; [2]University of Pittsburgh/UPMC, NSABP Foundation, Pittsburgh, USA; [3]Hospital General Universitario Gregorio Marañon, Universidad Complutense, CIBERONC, GEICAM, Madrid, Spain; [4]Dana-Farber Cancer Institute, Boston, USA; [5]Fudan University Shanghai Cancer Center, Shanghai, China; [6]University Hospital Erlangen, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [7]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [8]Grupo Medico Camino S.C., Mexico City, Mexico; [9]N.N.Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Mayo Clinic, Rochester; [11]Department of Medicine (Hematology/Oncology), University of California San Francisco, San Francisco, USA; [12]Department of Oncology & Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland; [13]Instituto D'Or de Pesquisa e Ensino (IDOR), Sao Paulo, Brazil; [14]Rigshospitalet, Copenhagen, Denmark; [15]National Cancer Center Hospital, Tokyo, Japan; [16]IRCSS Ospedale Policlinico San Martino, UO Breast Unit, Genoa; [17]Università di Genova, Department of Internal Medicine and Medical Specialties (DIM), Genoa, Italy; [18]Medical University of Vienna, Vienna, Austria; [19]Medizinische Hochschule Hannover, Hannover, Germany; [20]Clin. Pesq. e Centro São Paulo, São Paulo, Brazil; [21]Yonsei Cancer Center, Seoul, Korea; [22]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua; [23]Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; [24]International Breast Cancer Center (IBCC), Madrid & Barcelona, and Vall d'Hebron Institute of Oncology, Barcelona; [25]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville; [27]Eli Lilly and Company, Indianapolis, USA; [28]Kyoto University Hospital, Kyoto, Japan; [29]Royal Marsden NHS Foundation Trust, London, UK; [30]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, USA

On October 12, 2021, the FDA approved abemaciclib for adjuvant treatment of adult patients with HR+/HER2-, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test

The FDA also approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay as a companion diagnostic for selecting patients for this indication

1. Harbeck N et al. *Ann Oncol*. 2021;S0923-7534(21)04494-X.
2. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

Why Are the Results Different From Other Adjuvant Trials?

Aditya Bardia, MD, Discussion monarchE, ESMO VP, 2021

	PENELOPE-B[1]	PALLAS[2]	MONARCH-E[3]
Sample size	1,250	5,600	5,637
Study population	High risk	Moderate to high risk	High risk
Study drug (duration)	Palbociclib (1 year)	Palbociclib (2 years)	Abemaciclib (2 years)
IDFS results, HR (95%CI)	0.93 (0.76-1.15)	0.93 (0.74-1.17)	**0.69 (0.58-0.82)**
3-year IDFS (*P*)	81.2% vs 77.7% (NS)	88.2% vs 88.5% (NS)	**88.8% vs 83.4% (< .0001)**
Discontinuation rate, %	17.5	42.2	17.4
Duration of follow-up, mo	42.8	23.7	27.1

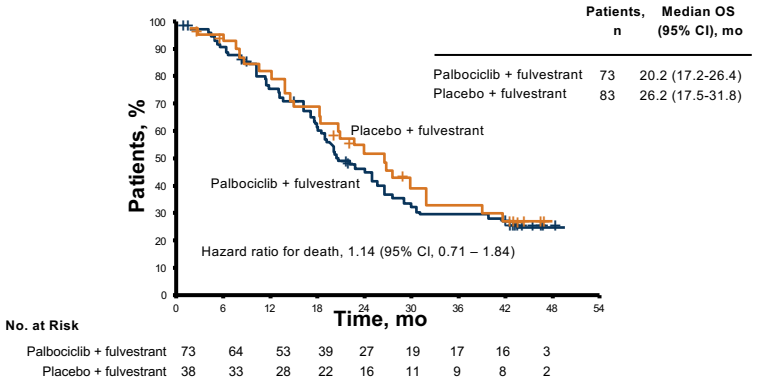
- **Higher-risk population:** In PALLAS, no benefit with palbociclib in patients with N2/N3 disease (HR = 0.89, 95%CI, 0.68-1.17); however, subset analysis, and need to exert appropriate caution
- **Discontinuation:** In PALLAS, no significant differences based on dose exposure noted; however, power limited by few events
- **Differences in drugs:** Continuous vs intermittent dosing in EBC vs MBC; spectrum and potency of kinome inhibition

1. Loibl S et al. *J Clin Oncol.* 2021;39:1518-1530. 2. Mayer EL et al. *Lancet Oncology*. 2021:22:212-222. 3. Harbeck N et al. *Ann Oncol*. 2021;S0923-7534(21)04494-X.

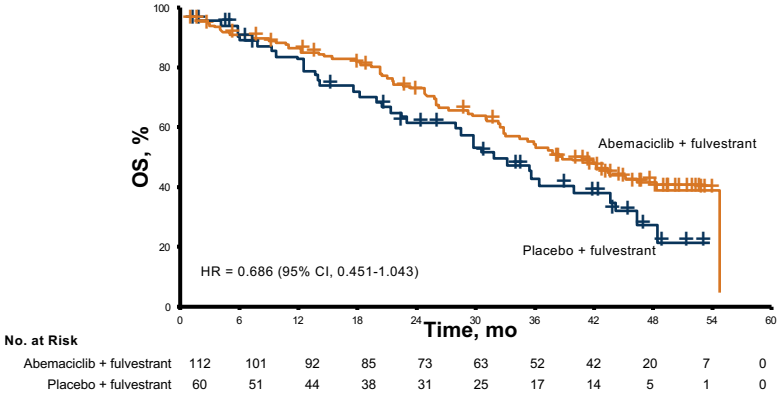
Abemaciclib vs Palbociclib: Primary Endocrine-Resistant Setting[1-4]

OS in Primary Endocrine-Resistant MBC

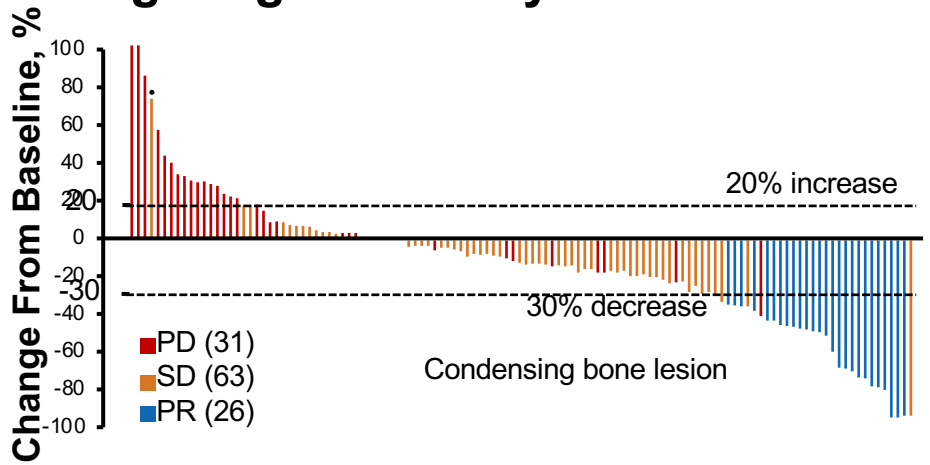
PALOMA-3



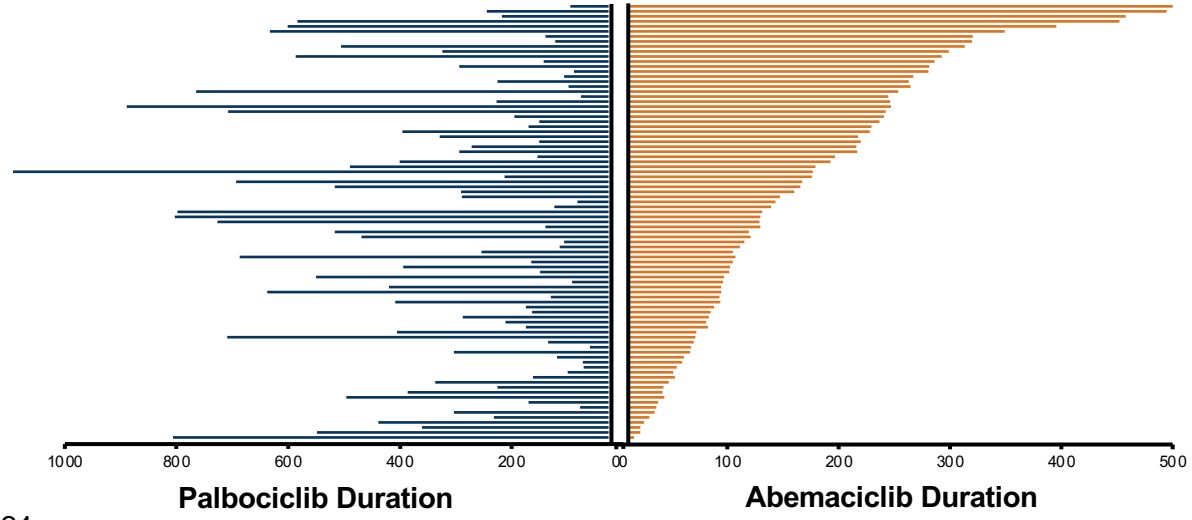
MONARCH 2



Single-Agent Activity With Abemaciclib



Clinical Benefit With Abemaciclib Post-Palbociclib



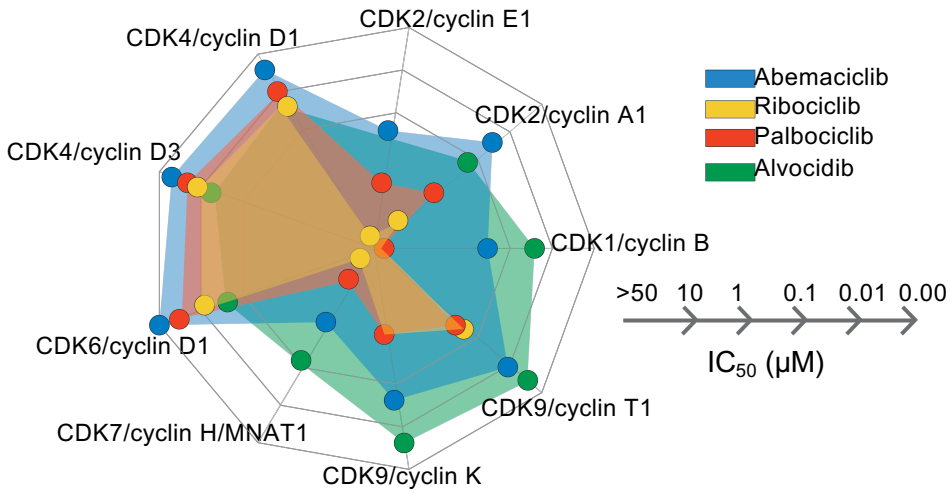
1. Turner NC et al. *N Engl J Med*. 2018;379:1926-1936. 2. Sledge GW et al. *JAMA Oncol*. 2020;6:116-124.
3. Dicklet MN et al. *Clin Cancer Res*. 2017;23:5218-5224. 4. Wander SA et al. *J Natl Compr Canc Netw*. 2021;1-8.

Aditya Bardia, MD, Discussion monarchE, ESMO VP, 2021

Abemaciclib vs Palbociclib: Molecular Differences[1,2]

Abemaciclib

Palbociclib

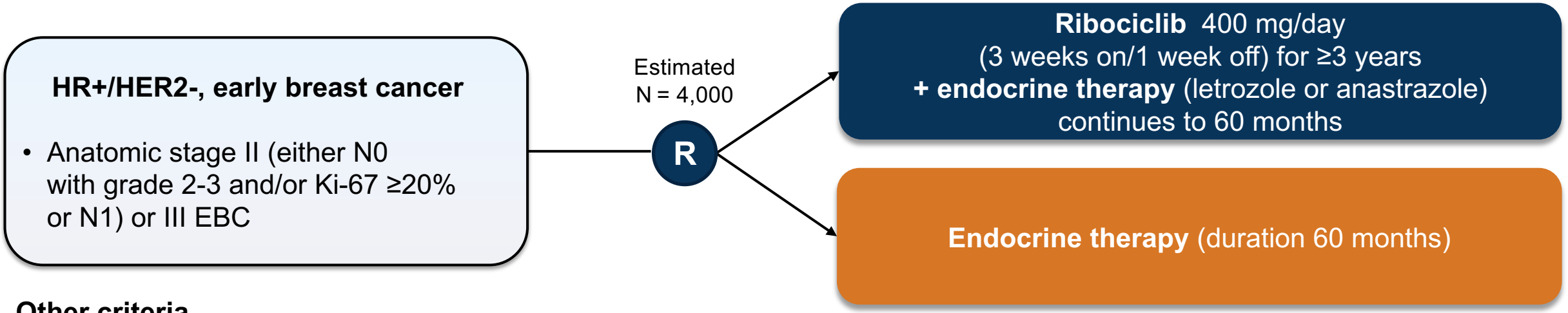


- Seemingly similar drugs, but there may be differences in different settings
- Deeper understanding of kinome differences might help identify novel targets
- Hypothesis generating, and ideally, we need a randomized clinical trial to compare the drugs (neoadjuvant?)

Chen P et al, Mol Cancer Ther 2016; Hafner M et al, Cell Chem Bio 2019

Aditya Bardia, MD, Discussion monarchE, ESMO VP, 2021

Ongoing Adjuvant CDK4 and 6 Inhibitor Trial: NATALEE[1]



Other criteria

- Women or men
- Pre-[a]/post-menopausal
- With or without prior adjuvant/neoadjuvant chemo
- No distant metastases

Primary objective: IDFS (STEEP criteria)

Key secondary objectives: RFS, distant DFS, OS, PROs, PK, and safety

[a] Premenopausal and male patients will also receive goserelin 3.6 mg/28 d.

1. Slamon et al. *J Clin Oncol.* 2019;37(suppl 15):TPS597-TPS597.