A step forward in treatment landscape for HR+, HER2- breast cancer patients

臺北榮民總醫院
Taipei Veterans General Hospital

Chun-Yu Liu

劉峻宇

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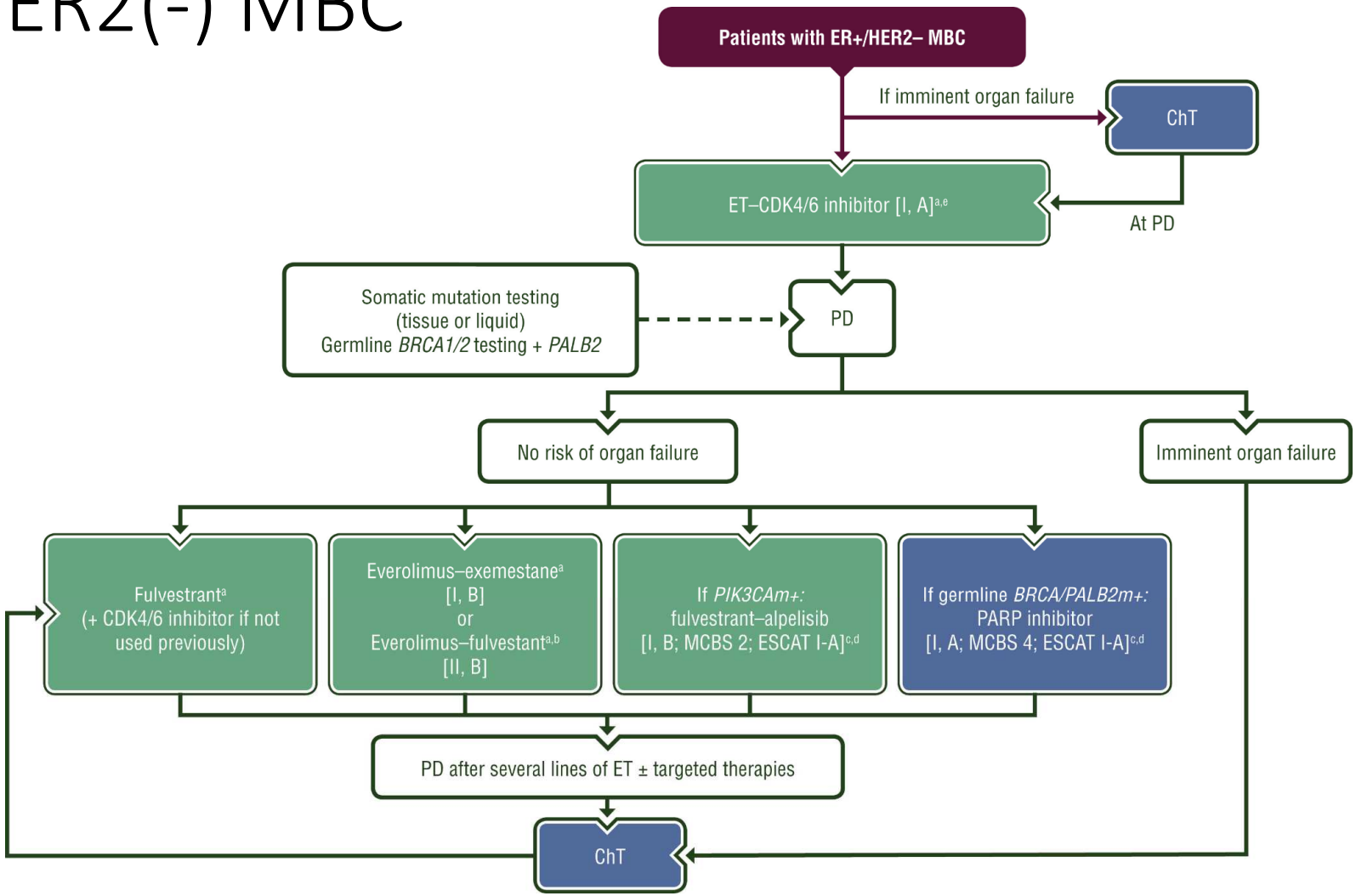
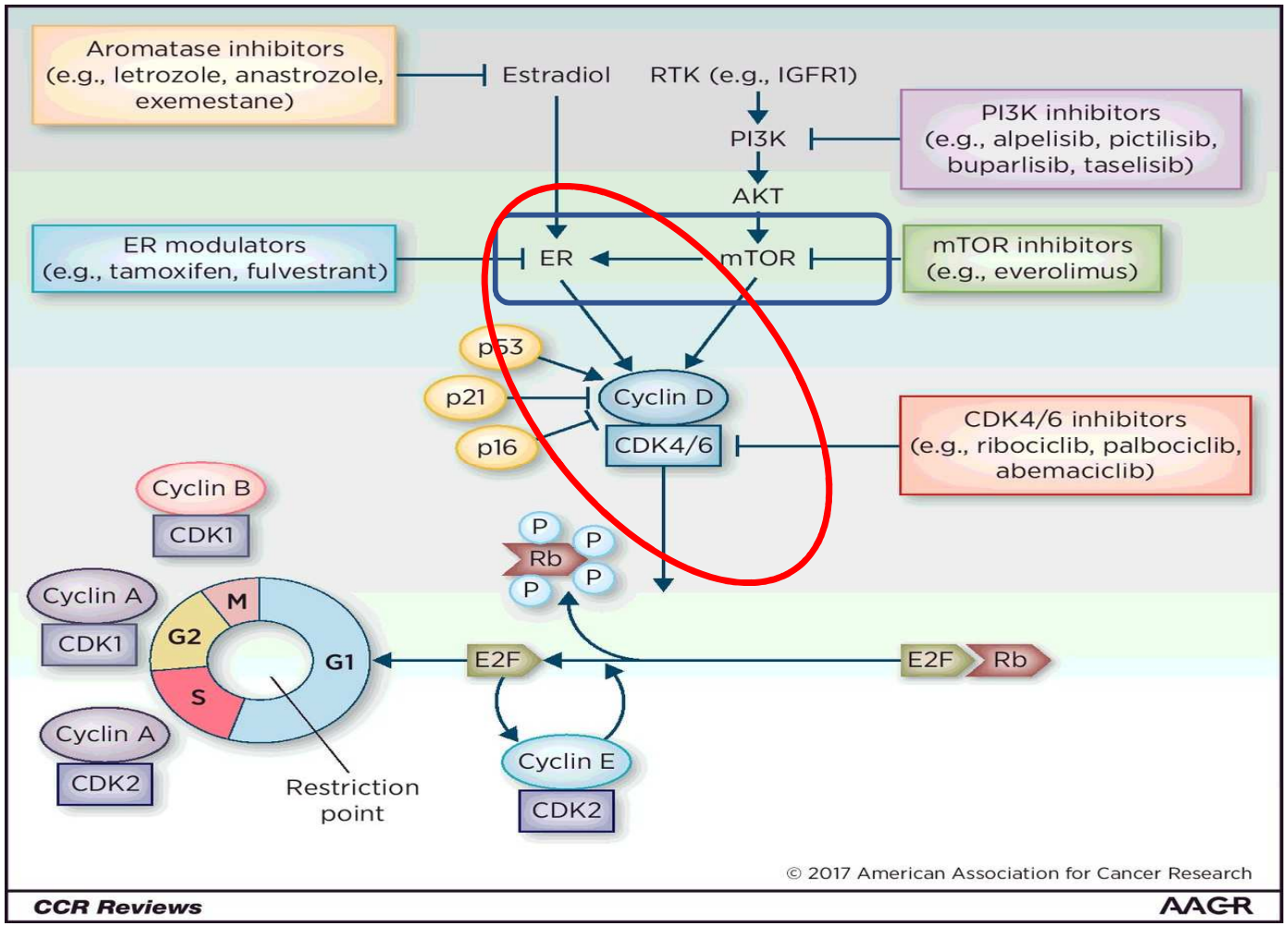
TPE-VGH Breast Cancer Center

ER(+)HER2(-) MBC



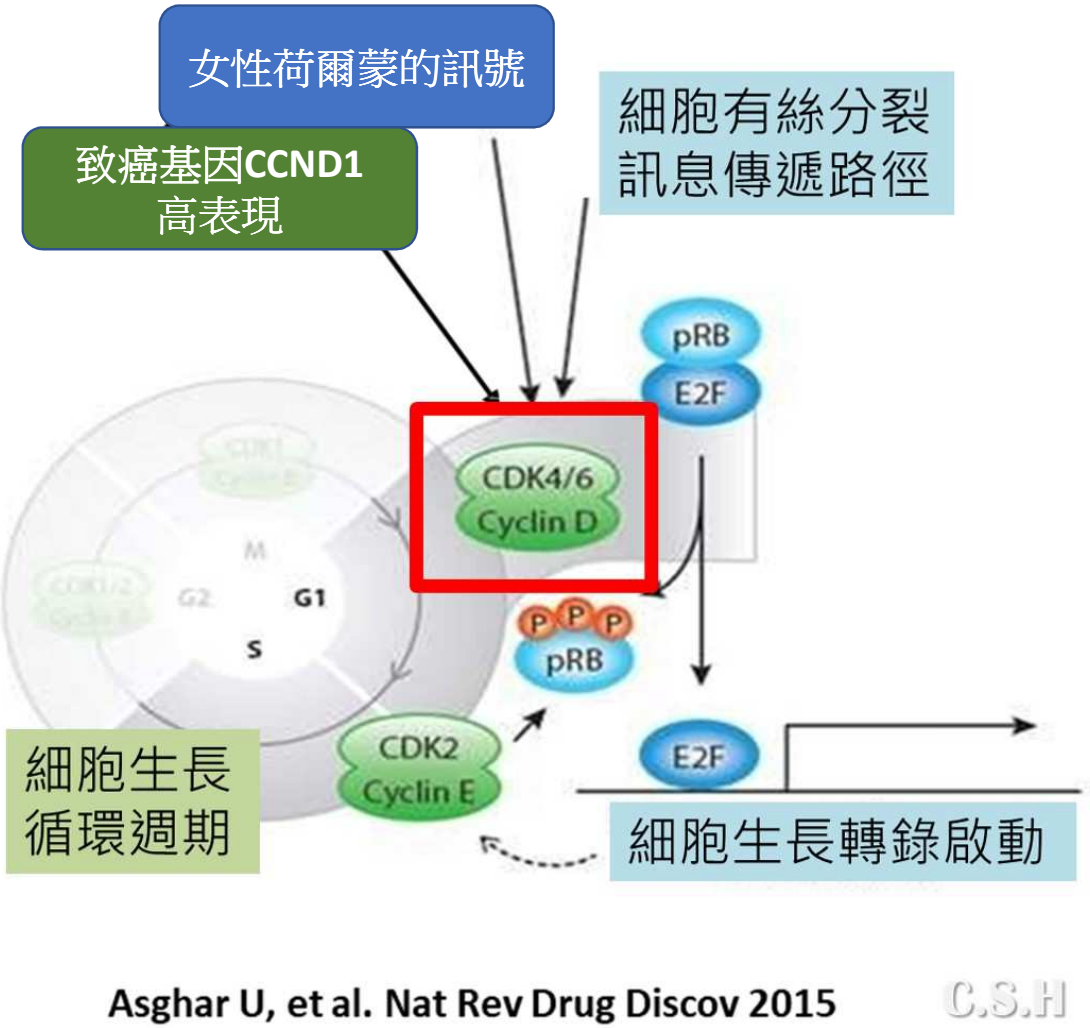
Ann Oncol. 2021 Dec;32(12):1475-1495.

ER signaling, cell cycle and mTOR: actionable targets



Debu Tripathy et al. Clin Cancer Res 2017;23:3251-3262

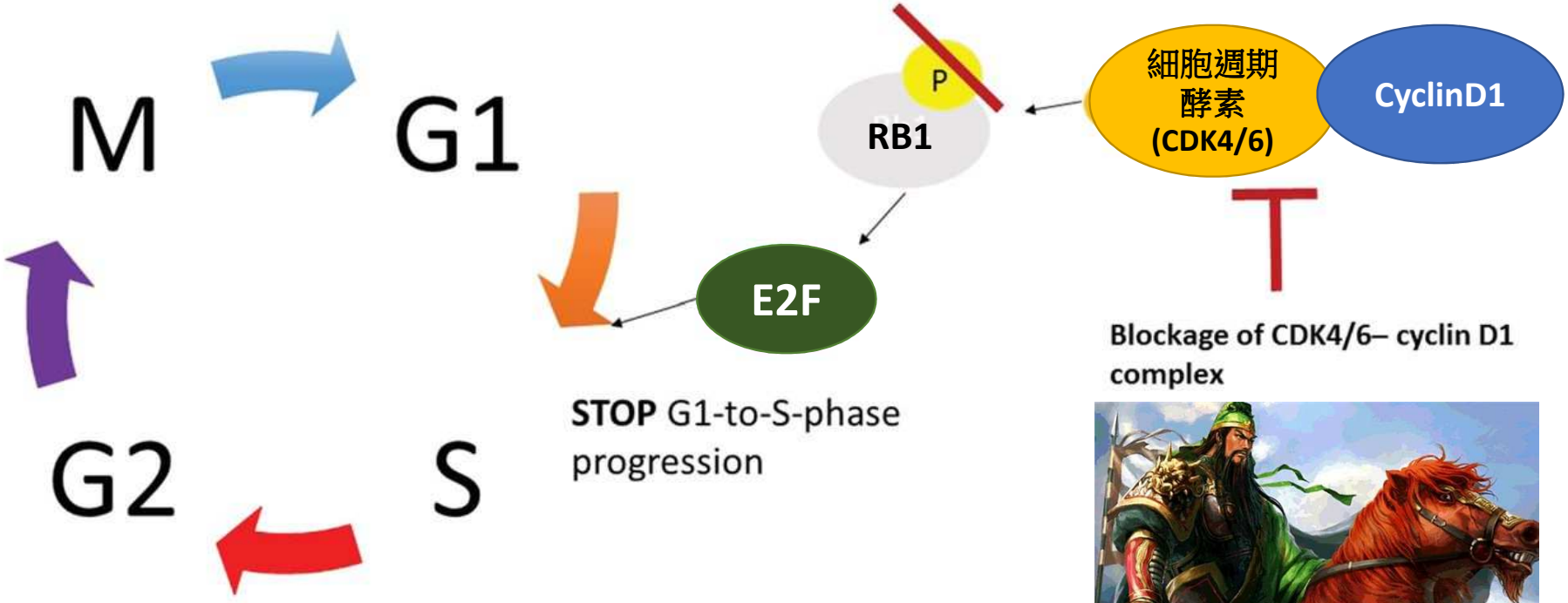
賀爾蒙刺激細胞周期運轉(加速分裂)



Asghar U, et al. Nat Rev Drug Discov 2015

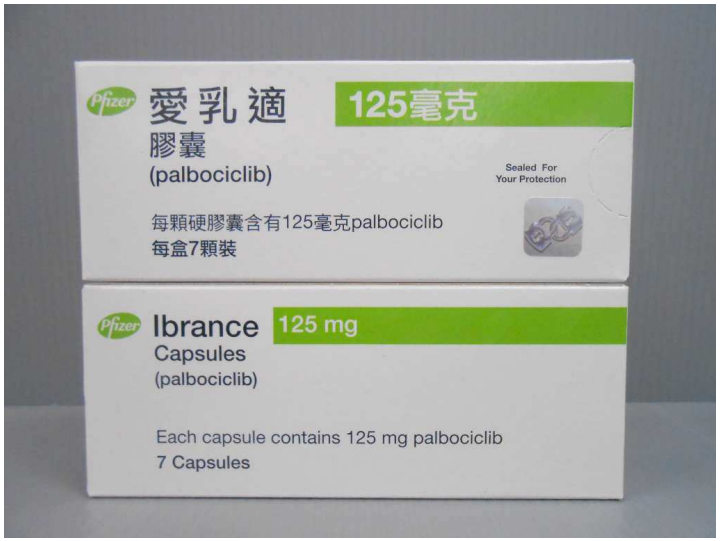
C.S.H

CDK4/6 抑制劑 (細胞週期激素4/6 抑制劑)



Preusser M, et al. ESMO Open 2019;3:e000368.

愛乳適 vs 擊癌利 vs 捷癌寧



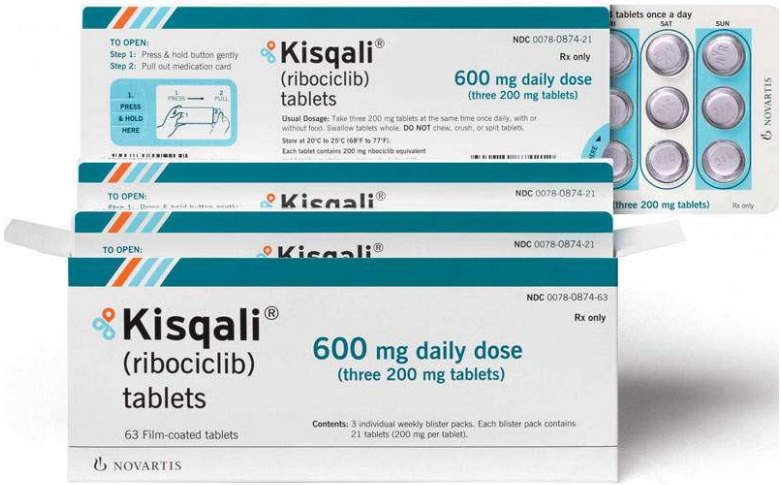
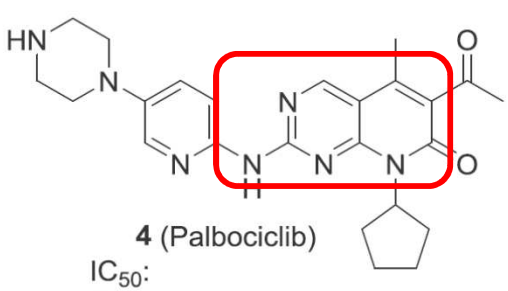


Table 1. Key characteristics of CDK inhibitors

Drug	Palbociclib (Pfizer) (PD0332991, Ibrance)	Ribociclib (Novartis) (LEE011)	Abemaciclib (Eli Lilly) (LY2835219)
IC_{50} (*in vitro* kinase assay, recombinant proteins)	CDK4 (D1): 11 nmol/L CDK4 (D3): 9 nmol/L CDK6 (D2): 15 nmol/L CDK1: >10 μmol/L CDK2: >10 μmol/L (66, 67)	CDK4: 10 nmol/L CDK6: 39 nmol/L CDK1: >100 μmol/L CDK2: >50 μmol/L (1, 89)	CDK4 (D1): 0.6–2 nmol/L CDK6 (D1): 2.4–5 nmol/L CDK 9: 57 nmol/L CDK1: >1 μmol/L CDK2: >500 nmol/L (1, 88)
PK	T_{max} 4.2–5.5 hr $t_{1/2}$ 25.9–26.7 hr (69, 70)	T_{max} 4 hr $t_{1/2}$ 24–36 hr (90, 91)	T_{max} 4–6 h $t_{1/2}$ 17–38 h (crosses blood:brain barrier; refs. 92, 93)
PD	Reduced RB phosphorylation in paired tumor biopsies, along with reduced fluorothymidine-PET uptake (75)	Reduced RB phosphorylation and Ki67 expression in paired tumor biopsies (90)	Reduced RB phosphorylation and topoisomerase IIα expression in paired tumor and skin biopsies (92)
Dosing	125 mg daily (3 weeks, 1-week drug holiday) or 200 mg daily (2 weeks, 1-week drug holiday; refs. 69, 70)	600 mg daily (3 weeks, 1-week drug holiday; ref. 90)	200 mg twice daily (continuous dosing; ref. 92)
Major dose-limiting toxicities	Neutropenia, thrombocytopenia	Neutropenia, thrombocytopenia	Fatigue
Other reported adverse events	Anemia, nausea, anorexia, fatigue, diarrhea (69, 70)	Mucositis Prolonged EKG QTc interval Elevated creatinine Nausea (90)	Diarrhea Neutropenia (92)

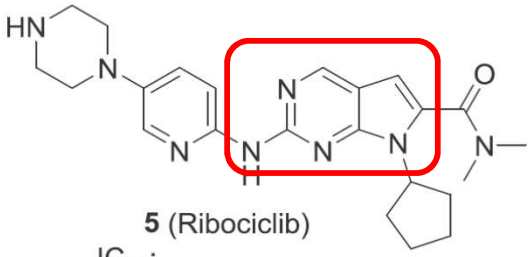
Cancer Discov. 2016 Apr;6(4):353-67.

Differential selectivity on CDKs



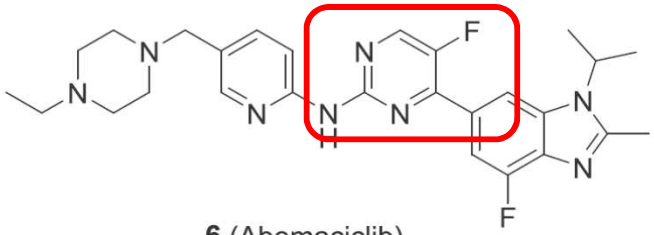
4 (Palbociclib)

IC_{50}:
CDK1: >10 μM
CDK2: >10 μM
CDK4: 9-11 nM
CDK5: >10 μM
CDK6: 15 nM
CDK7: ND
CDK9: ND



5 (Ribociclib)

IC_{50}:
CDK1: >100 μM
CDK2: >50 μM
CDK4: 10 nM
CDK5: ND
CDK6: 39 nM
CDK7: ND
CDK9: ND



6 (Abemaciclib)

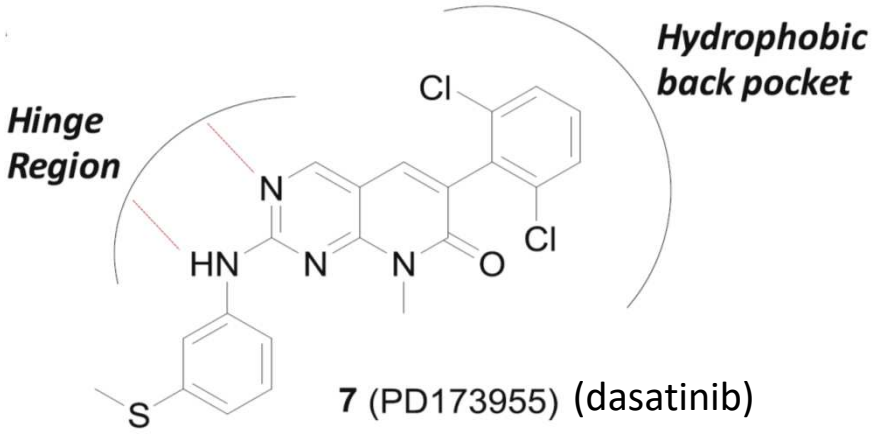
IC_{50}:
CDK1: >1 μM
CDK2: >500 nM
CDK4: 2 nM
CDK5: ND
CDK6: 5 nM
CDK7: 300 nM
CDK9: 57 nM

Fig. 1. Examples of chemical structure and CDKs inhibitory activity of first (A), second (B) and third (C) generation compounds.

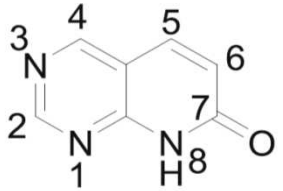
Molecules 2021, 26, 1488

ATP-competing kinase inhibitor scaffold

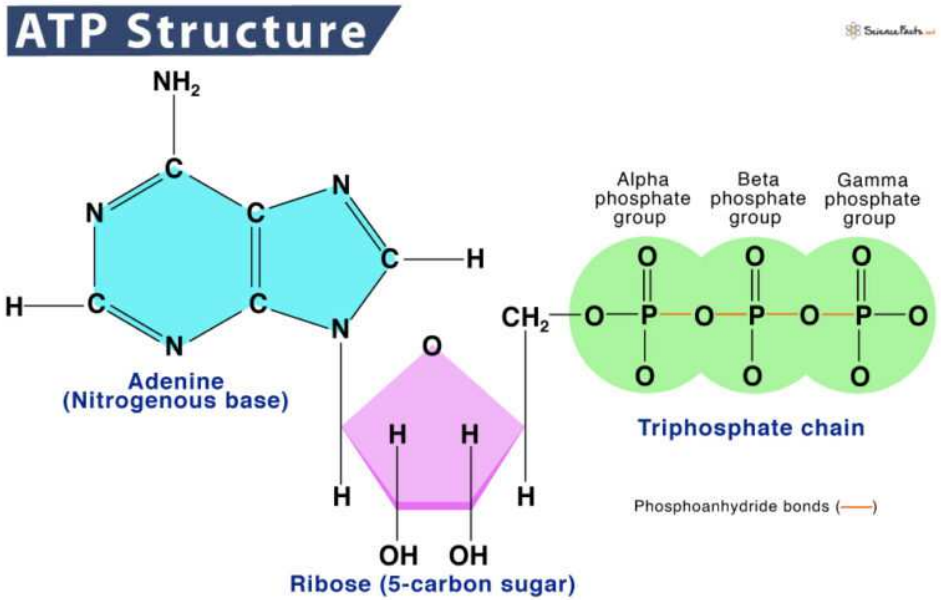
Example of a ATP-binding pocket of Abl kinase



7 (PD173955) (dasatinib)



pyrido[2,3-d]pyrimidin-7-one



https://www.sciencefacts.net/wp-content/uploads/2021/12/Adenosine-Triphosphate-ATP-Structure-768x494.jpg

European Journal of Medicinal Chemistry 172 (2019) 143e153

Example of a ATP-competing CDK4/CDK6 inhibitor and structure activity relationship

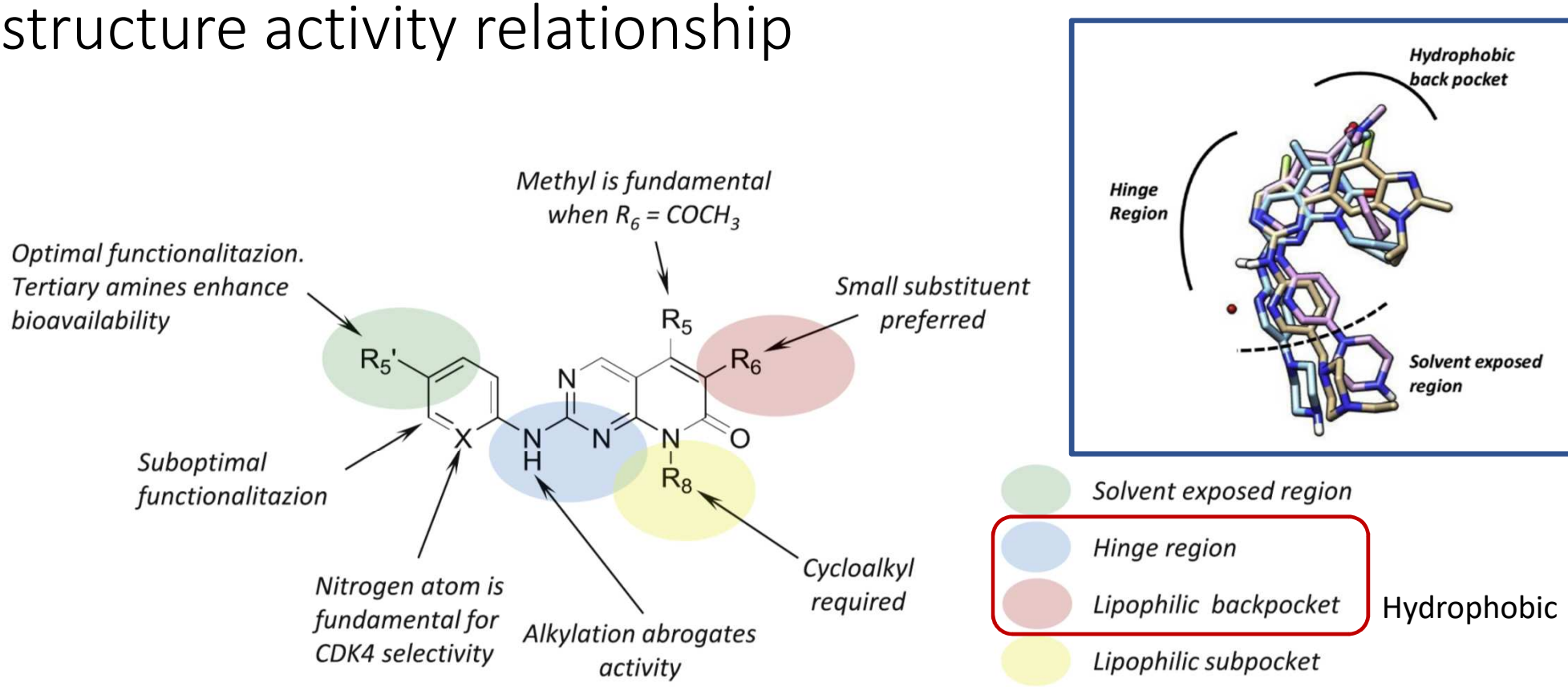


Fig. 4. SAR for Palbociclib in context with the main features of ATP binding site.

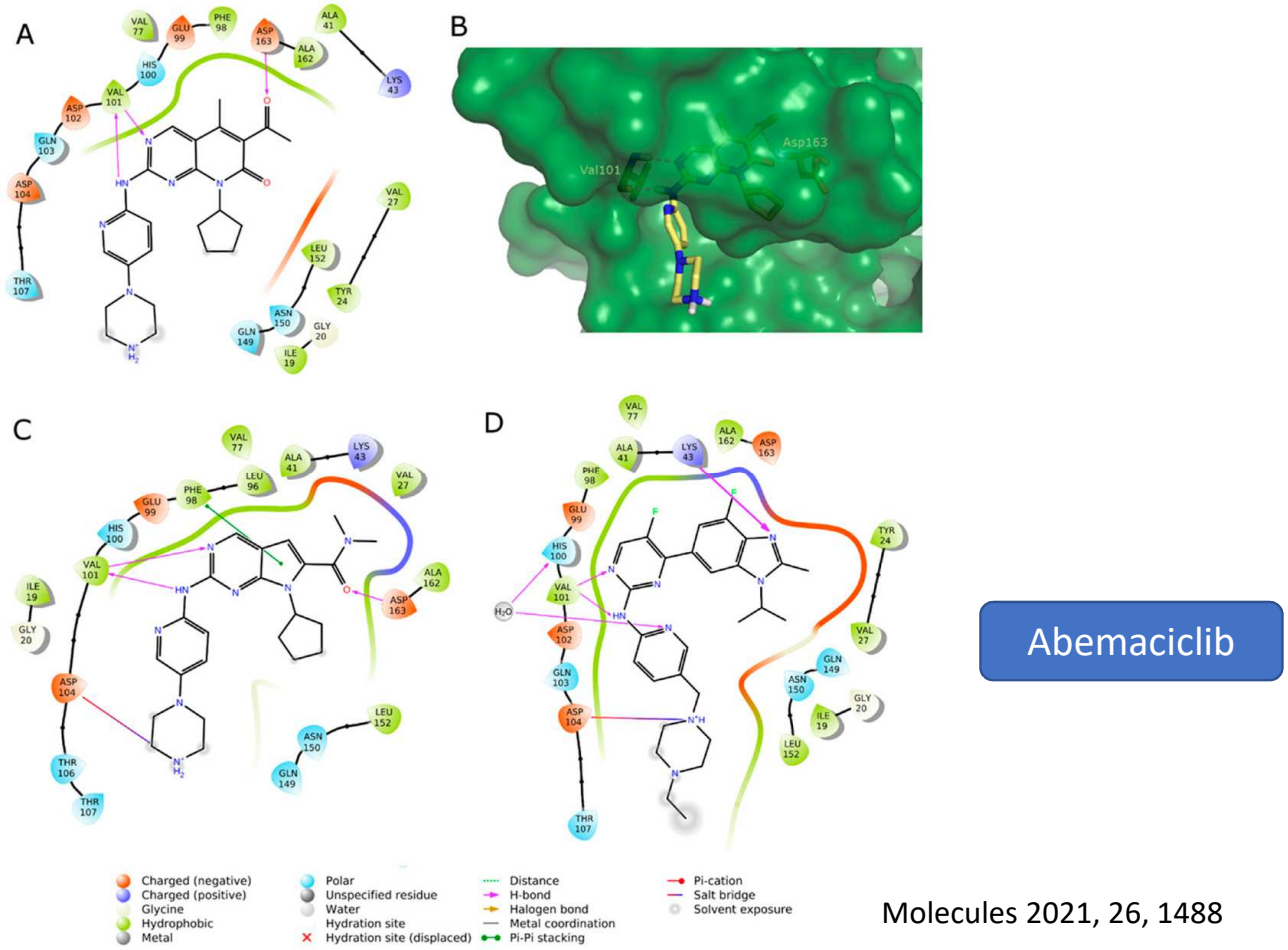
European Journal of Medicinal Chemistry 172 (2019) 143e153

Effectively inhibiting CDK4/CDK6 by competing the ATP-binding pocket

Palbociclib

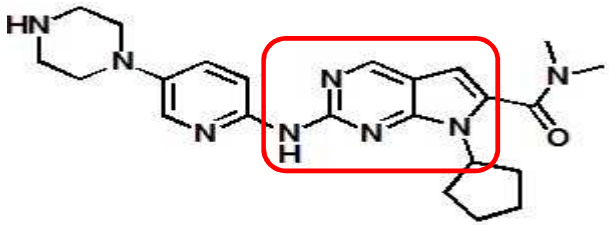
Ribociclib

Abemaciclib

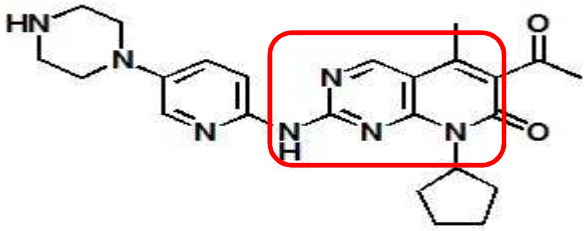


Molecules 2021, 26, 1488

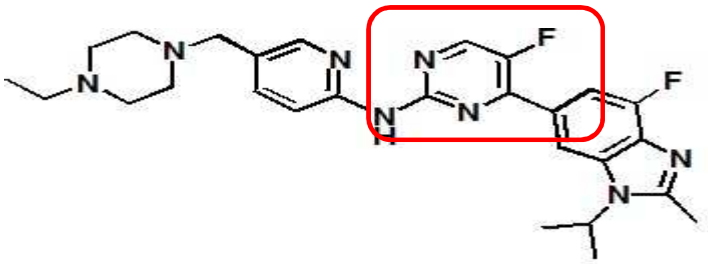
Are these differences meaningful?



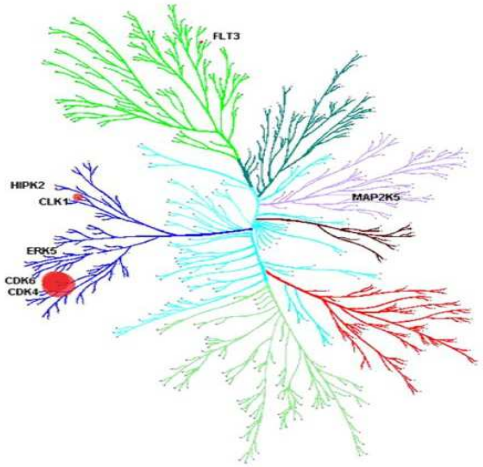
LEE011
CDK 4/6 inhibitor
breast cancer
Novartis



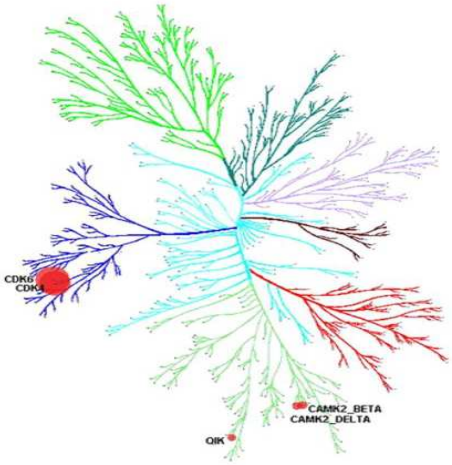
Palbociclib
CDK 4/6 inhibitor
breast cancer
Pfizer



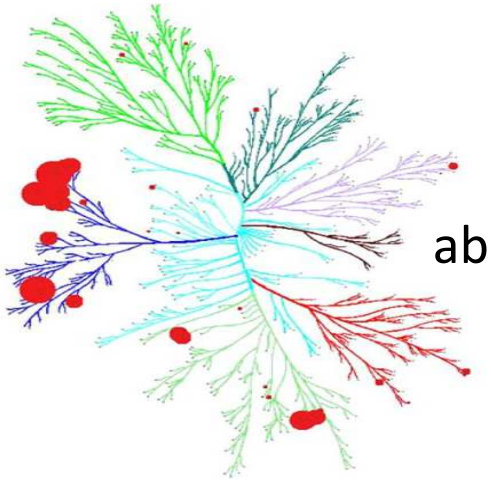
Bemaciclib
LY2835219
CDK4/6 inhibitor
Breast Cancer
Eli Lilly



Palbociclib



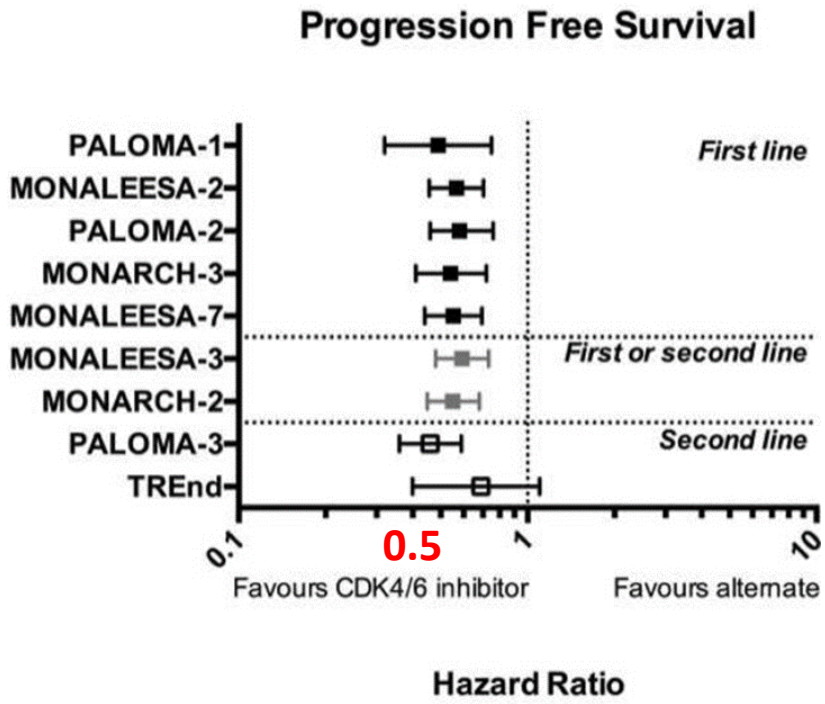
Ribociclib



abemaciclib

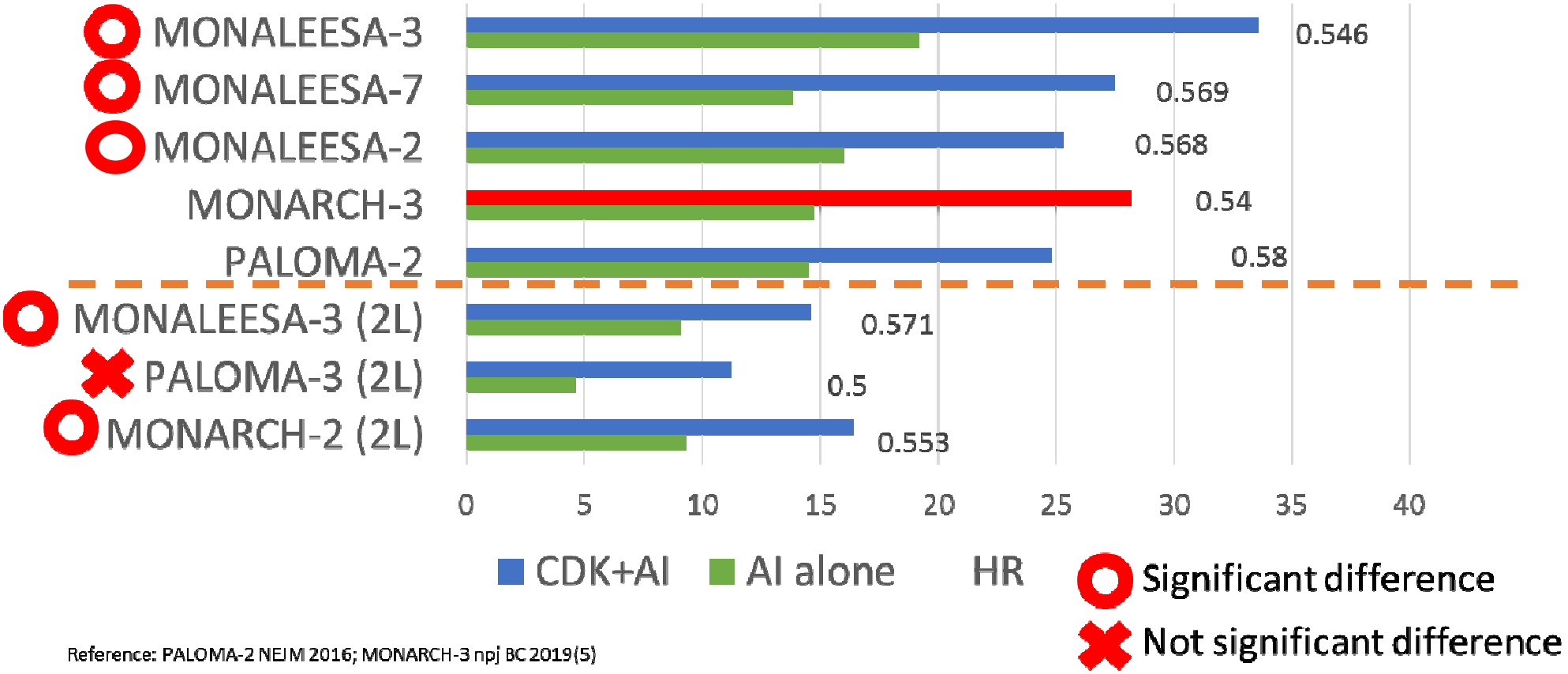
Chen Ping et al. MTC 2016

Similar hazard ratios of PFS of CDK 4/6 inhibitors-endocrine combination in ER+/HER2- metastatic breast cancer 1L/2L treatments



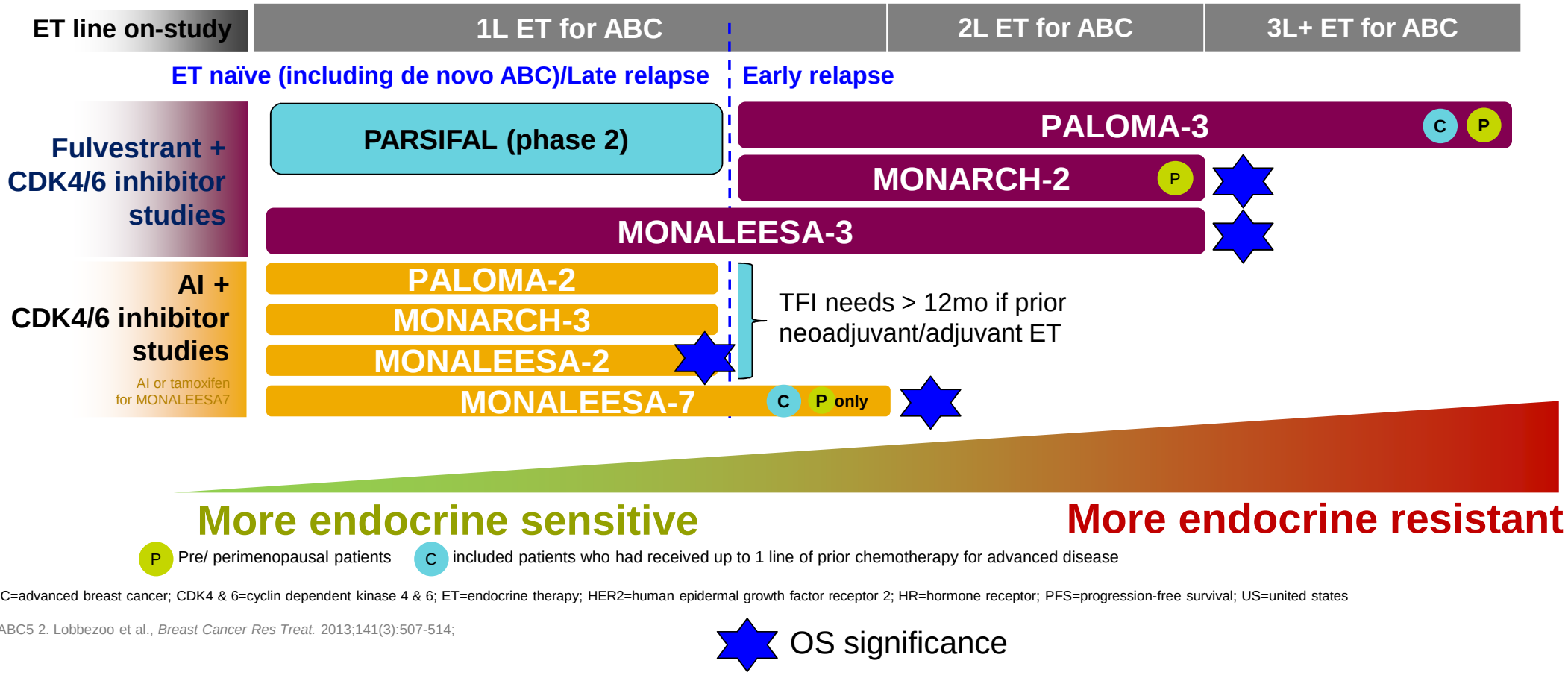
Asia Pac J Clin Oncol. 2018 Oct;14 Suppl 4:3-11.

OS data are different in statistics



Reference: PALOMA-2 NEJM 2016; MONARCH-3 npj BC 2019(5)

Current landscape of endocrine therapy and CDK4/6 inhibitors in the HR+/HER2- ABC



P Pre/ perimenopausal patients C included patients who had received up to 1 line of prior chemotherapy for advanced disease

ABC=advanced breast cancer; CDK4 & 6=cyclin dependent kinase 4 & 6; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; PFS=progression-free survival; US=united states

1. ABC5 2. Lobbezoo et al., *Breast Cancer Res Treat.* 2013;141(3):507-514;

OS significance

Defining high risk groups for ER(+)/HER2(-) early breast cancer

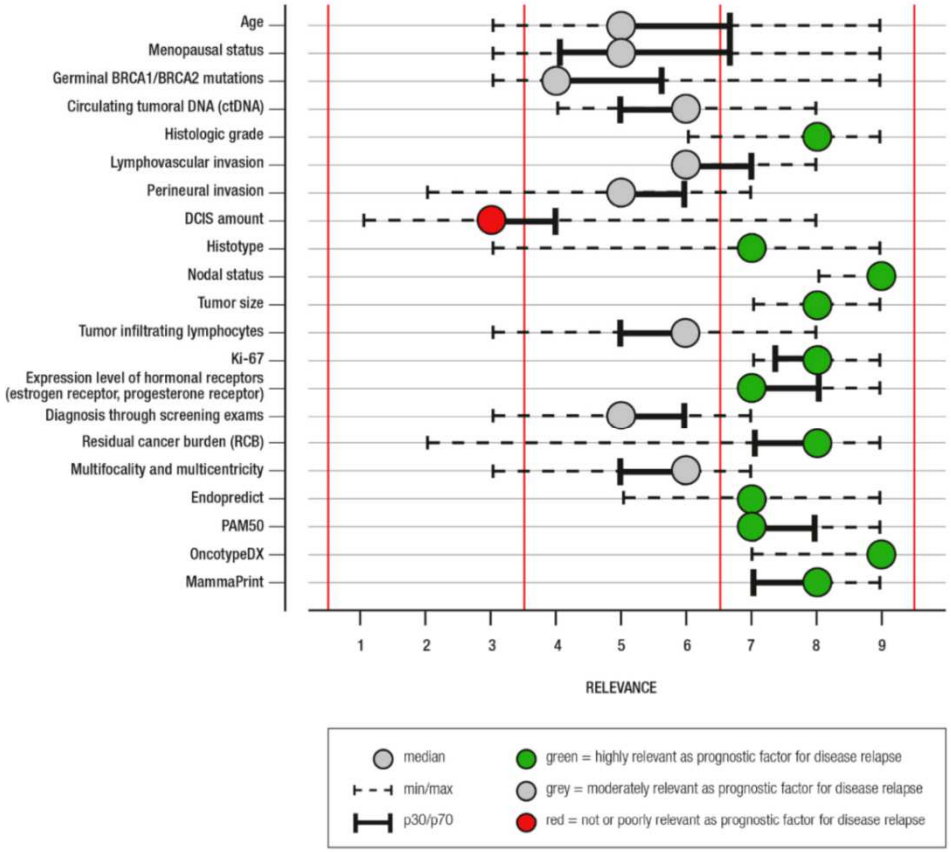


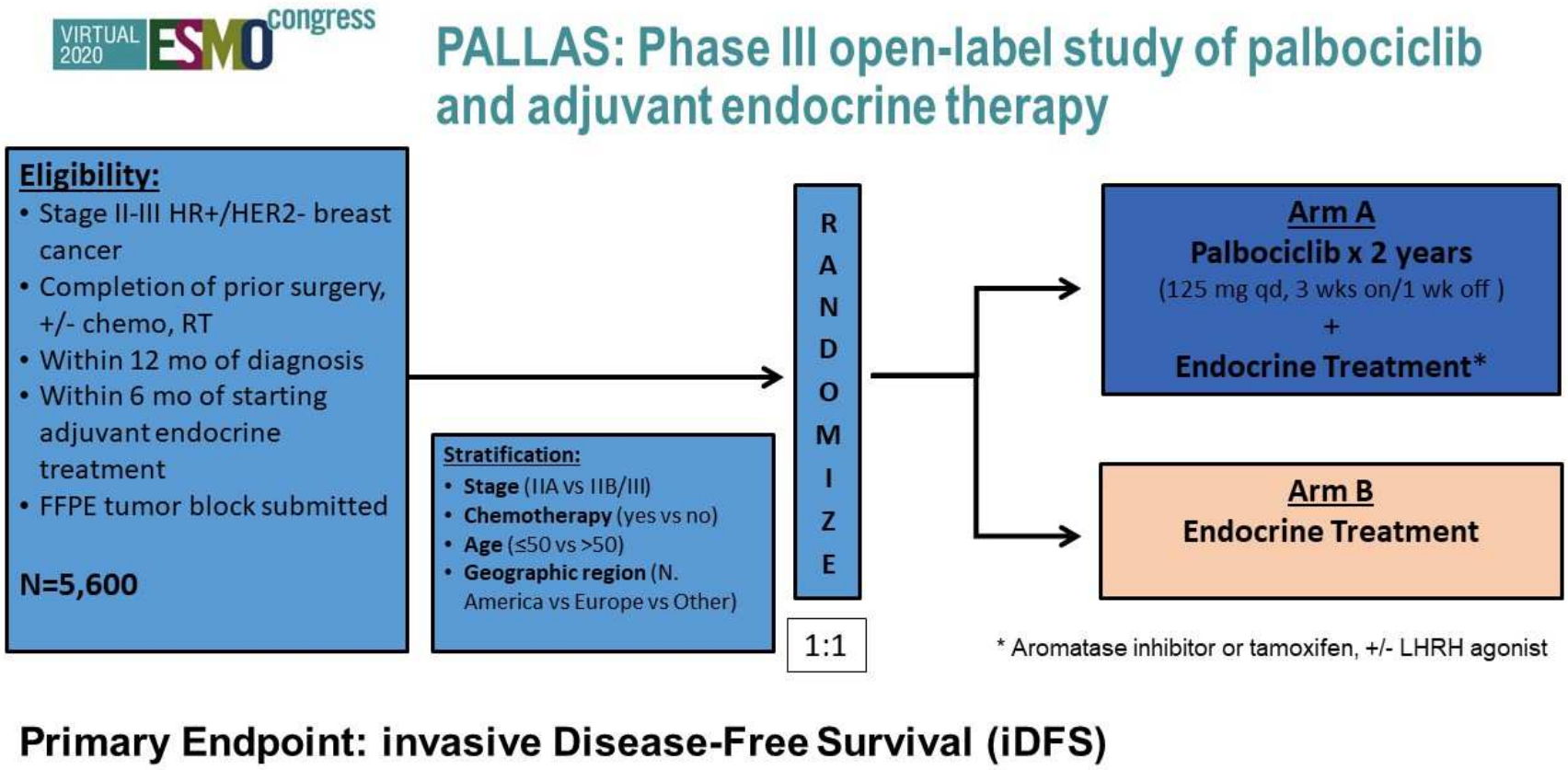
Table 2. Synoptic table of risk factors for disease relapse.

Factor	High Risk	Low Risk
Grade	3	1
Histotype	n/a	Pure tubular, pure mucinous, pure cribriform
Tumor size	T3/4	T1
Nodal status	N2/N3	N0
Ki-67	>30%	<20%
Expression level of hormonal receptors (ER, PgR)	ER <10% and/or PgR <20%	n/a
Residual cancer burden	RCB-III	RCB-0
Genomic signature (Oncotype DX, MammaPrint®, EndoPredict®, PAM50)	High-risk class	Low-risk class

n/a: not available, RCB: residual cancer burden.

Cancers 2022, 14, 1898.

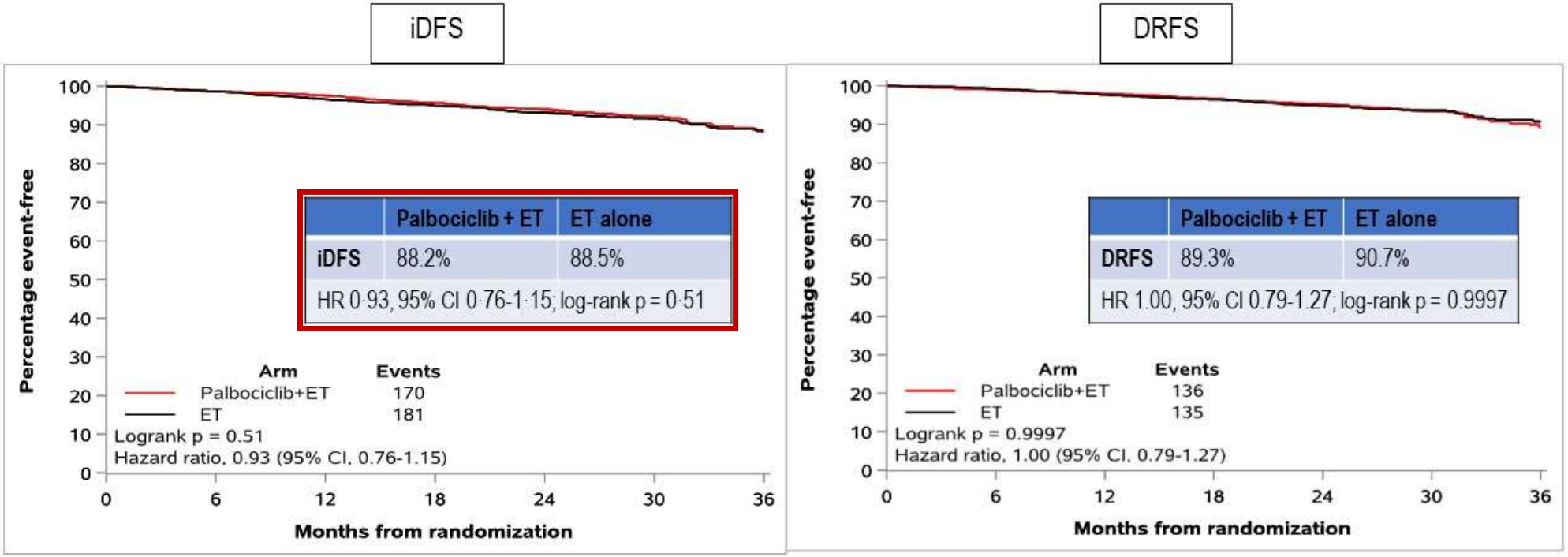
Can Palbociclib add more benefit to adjuvant ET?



Adjuvant palbociclib is not beneficiary

VIRTUAL 2020 ESMO congress

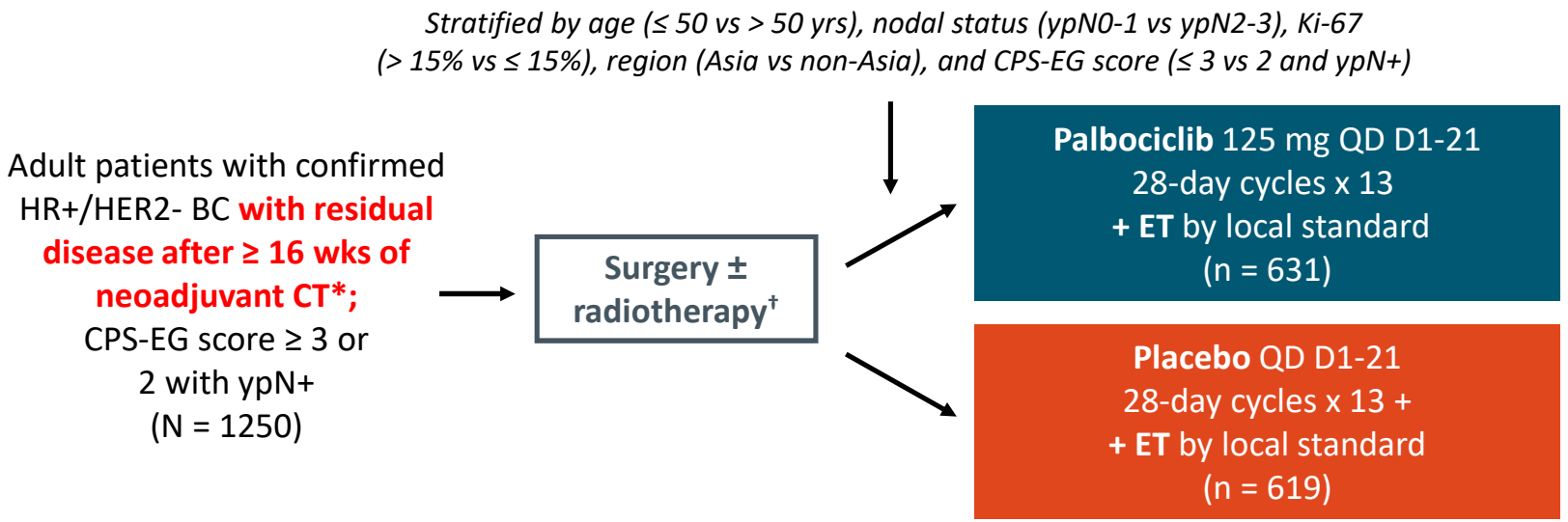
PALLAS: Primary Endpoint iDFS



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

PENELOPE-B: Palbociclib + ET in HR+/HER2- BC at High Risk of Relapse After Neoadjuvant Chemotherapy

- Randomized, double-blind, placebo-controlled phase III trial



*Includes 6 wks of taxanes.
†Time between locoregional therapy and randomization: < 16 wks from final surgery or < 10 wks from RT completion.

- Primary endpoint: iDFS
- Secondary endpoints include: iDFS excluding second primary invasive non-breast cancers, distant DFS, locoregional RFS, OS, safety, compliance, QoL

Loibl. SABCS 2020. Abstr GS1-02.

Slide credit: clinicaloptions.com

PENELOPE-B: Baseline Characteristics

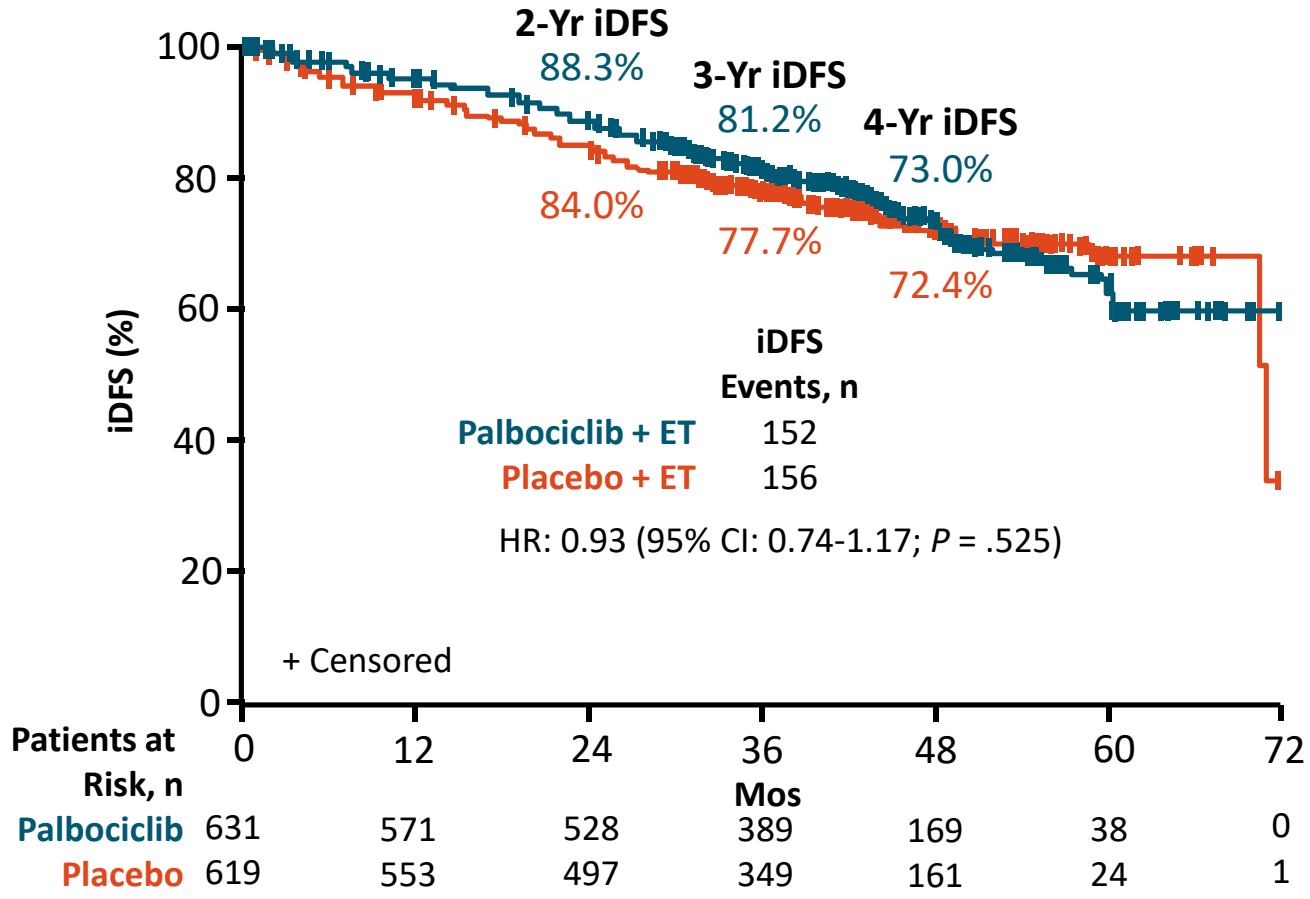
Characteristic	Palbociclib (n = 631)	Placebo (n = 619)
Median age, yrs (range)	49 (22-76)	48 (19-79)
▪ ≤ 50 yrs, %	55.9	56.2
Histological lymph node status at surgery, %		
▪ ypN0-1	49.1	50.1
▪ ypN2-3	50.9	49.9
Ki-67 >15% by central pathology, %	25.5	25.5
CPS-EG score, %		
▪ 2 and ypN+	40.1	41.2
▪ ≥ 3	59.9	58.8

Characteristic	Palbociclib (n = 631)	Placebo (n = 619)
Tumor stage at surgery, %		
▪ ypT0-1	37.7	33.7
▪ ypT2-3	58.3	62.9
▪ ypT4	4.0	3.4
Lobular histology, %	9.2	8.5
G3 grading, %	46.7	48.1
Ovarian ablation, %	17.1	18.3
Tamoxifen, %	49.8	49.8

Loibl. SABCS 2020. Abstr GS1-02.

Slide credit: clinicaloptions.com

PENELOPE-B: iDFS (Primary Endpoint)



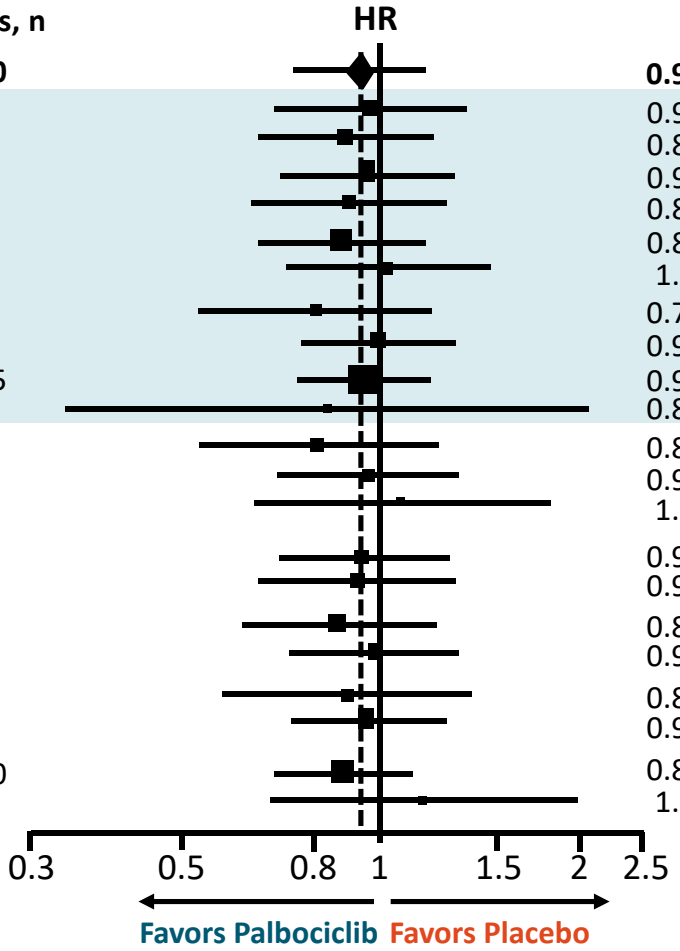
Loibl. SABCS 2020. Abstr GS1-02. Reproduced with permission.

- Median f/u: 42.8 mos
- Types of iDFS events
  - 74% distant recurrences
    - 116 with palbociclib, 111 with placebo
  - 16% invasive locoregional recurrences
    - 21 with palbociclib, 27 with placebo

Slide credit: clinicaloptions.com

PENELOPE-B: iDFS by Subgroup

Subgroup		Patients, n	HR (95% CI)	*P* Value	Interaction Test
Overall		**1250**	**0.931 (0.744-1.16)**	**.532**	
ypN	0-1	620	0.974 (0.696-1.36)	.880	.714
	2-3	630	0.891 (0.660-1.20)	.451	
Age, yrs	≤ 50	701	0.955 (0.709-1.29)	.764	.795
	> 50	549	0.899 (0.641-1.26)	.539	
Ki-67	≤ 15%	931	0.873 (0.654-1.16)	.355	.504
	> 15%	319	1.02 (0.718-1.46)	.895	
Risk status	CPS-EG score 2 and ypN+	508	0.798 (0.534-1.19)	.272	.389
	CPS-EG score ≥ 3	742	0.996 (0.760-1.30)	.976	
Geographical region	Non-Asian	1155	0.943 (0.749-1.19)	.619	.833
	Asian	95	0.836 (0.339-2.06)	.697	
CPS-EG score	1/2	497	0.810 (0.539-1.22)	.311	.674
	3	561	0.958 (0.697-1.31)	.789	
	4/5	192	1.08 (0.648-1.79)	.772	
First ET	Tamoxifen ± OFS	622	0.942 (0.698-1.27)	.698	.924
	AI ± OFS	628	0.927 (0.661-1.30)	.659	
Duration of CT	Shorter (≤ 20 wks)	594	0.867 (0.621-1.21)	.401	.596
	Longer (> 20 wks)	656	0.982 (0.726-1.33)	.904	
Type of surgery	Breast conserving	432	0.893 (0.580-1.37)	.605	.716
	Mastectomy	818	0.956 (0.736-1.24)	.738	
Overall response to NACT	CR or PR	1050	0.876 (0.683-1.12)	.297	.346
	SD or PD	200	1.16 (0.682-1.98)	.579	



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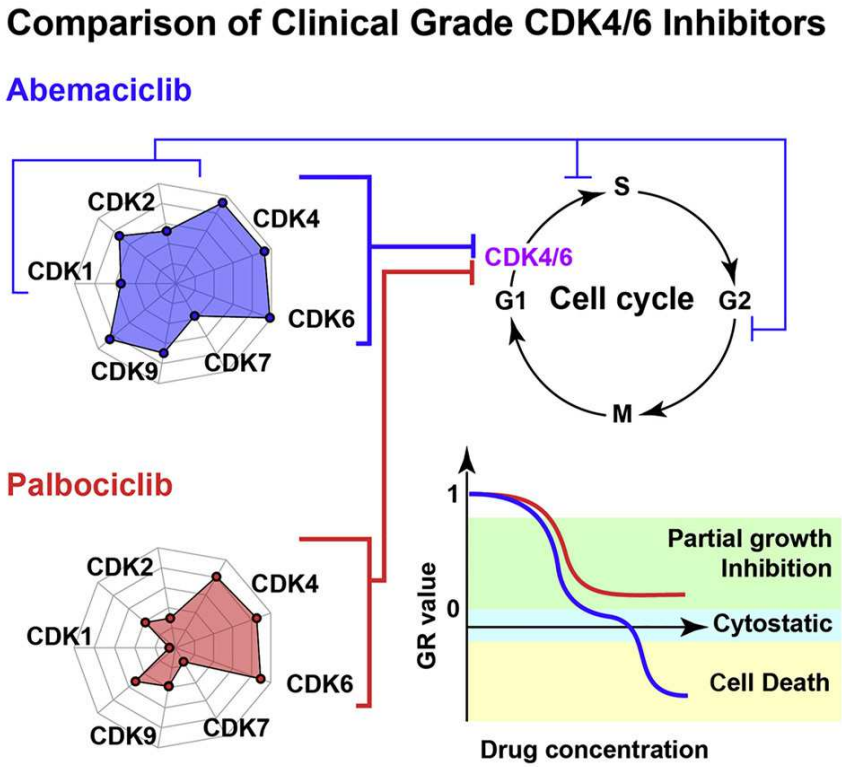
Off-”CDK4/6 effects” of abemaciclib

- Three approved CDK4/6 inhibitors have significantly different target spectra
- Secondary targets of abemaciclib include CDK1-cyclin B and CDK2-cyclin A/E complexes
- Only abemaciclib induces G2 cell-cycle arrest and a pan-CDK transcriptional signature
- Palbociclib-resistant and -adapted cells respond to abemaciclib but not ribociclib



Cell Chem Biol. 2019 Aug 15;26(8):1067-1080.e8

Responsiveness to CDK4/6i + ET in ET-sensitive & non-visceral crisis (1st-Line MBC)

Best overall response

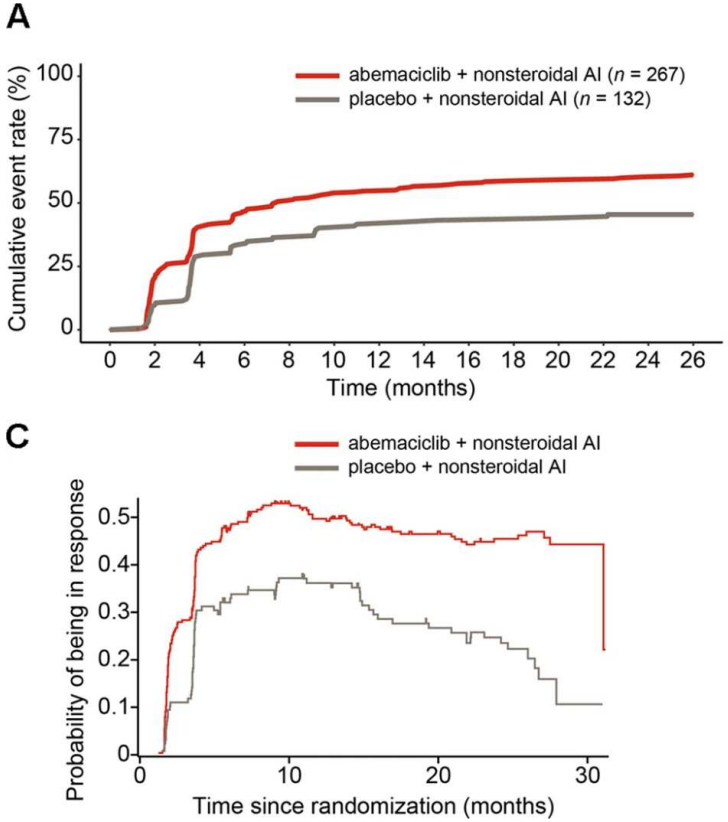
Abemaciclib + ET (48.2%) vs ET (34.5%)

Table 2. Best Overall Response

Best Overall Response*	Abemaciclib Plus Nonsteroidal AI		Placebo Plus Nonsteroidal AI	
	No. (%)	95% CI†	No. (%)	95% CI†
All patients	328 (100.0)		165 (100.0)	
Complete response	5 (1.5)	0.2 to 2.9	0 (0.0)	NA
Partial response	153 (46.6)	41.2 to 52.0	57 (34.5)	27.3 to 41.8
Stable disease	133 (40.5)	35.2 to 45.9	86 (52.1)	44.5 to 59.7
≥ 6 months	98 (29.9)	24.9 to 34.8	61 (37.0)	29.6 to 44.3
Progressive disease	14 (4.3)	2.1 to 6.5	12 (7.3)	3.3 to 11.2
Not evaluable	23 (7.0)	4.2 to 9.8	10 (6.1)	2.4 to 9.7
Objective response rate‡	158 (48.2)	42.8 to 53.6	57 (34.5)	27.3 to 41.8
Clinical benefit rate§	256 (78.0)	73.6 to 82.5	118 (71.5)	64.6 to 78.4

J Clin Oncol 2017; 35:3638-3646
npj Breast Cancer 2019; **5,** 5

Time to response (4-6 months)

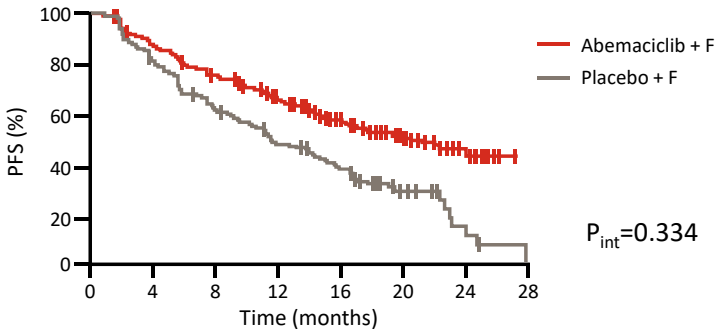


MONARCH 2/3 Subgroup Analysis by Liver Metastases

MONARCH 2

Abema + Ful (MBC 2L)

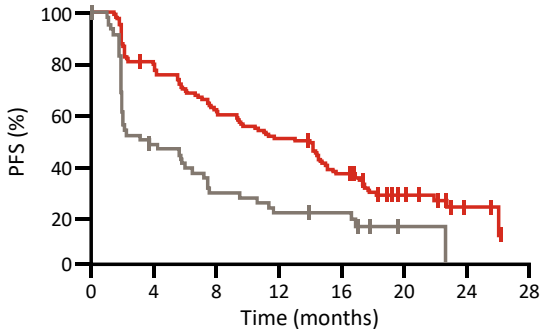
Liver Metastases – No



P_{int}=0.334

	Abemaciclib + F		Placebo + F		HR/ Change in ORR
	n	Estimate	n	Estimate	
PFS (ITT)	331	20.0 m	164	11.6 m	HR 0.555
ORR (MD)	207	47.8%	105	24.8%	+23.1%

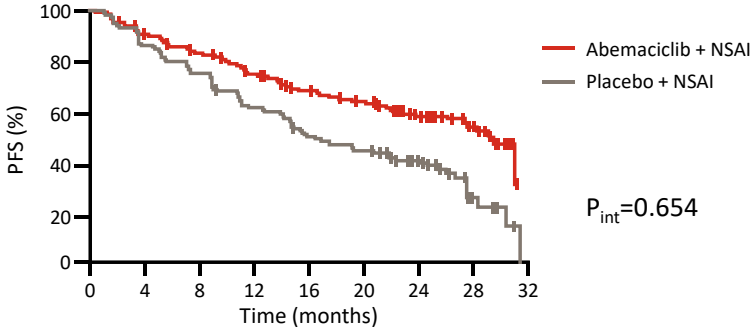
Liver Metastases – Yes



	Abemaciclib + F		Placebo + F		HR/ Change in ORR
	n	Estimate	n	Estimate	
PFS (ITT)	115	11.6 m	59	3.1 m	HR 0.447
ORR (MD)	111	48.7%	59	15.3%	+33.4%

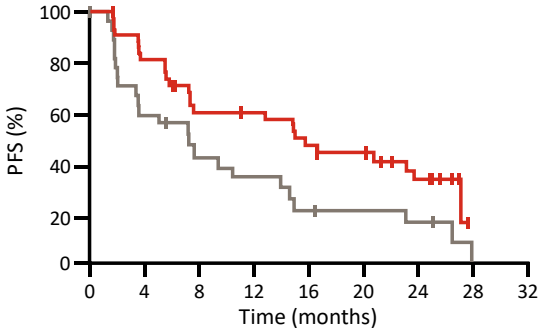
MONARCH 3

Abema + NSAI (MBC 1L)



P_{int}=0.654

	Abemaciclib + NSAI		Placebo + NSAI		HR/ Change in ORR
	n	Estimate	n	Estimate	
PFS (ITT)	281	29.5 m	134	16.5 m	HR 0.551
ORR (MD)	220	61.8%	102	52.9%	+8.9%



	Abemaciclib + NSAI		Placebo + NSAI		HR/ Change in ORR
	n	Estimate	n	Estimate	
PFS (ITT)	47	15.0 m	31	7.2 m	HR 0.477
ORR (MD)	47	57.5%	30	20.0%	+37.5%

O'Shaughnessy J, et al. *Cancer Res* 2018;78(suppl 13):Abstract CT099.

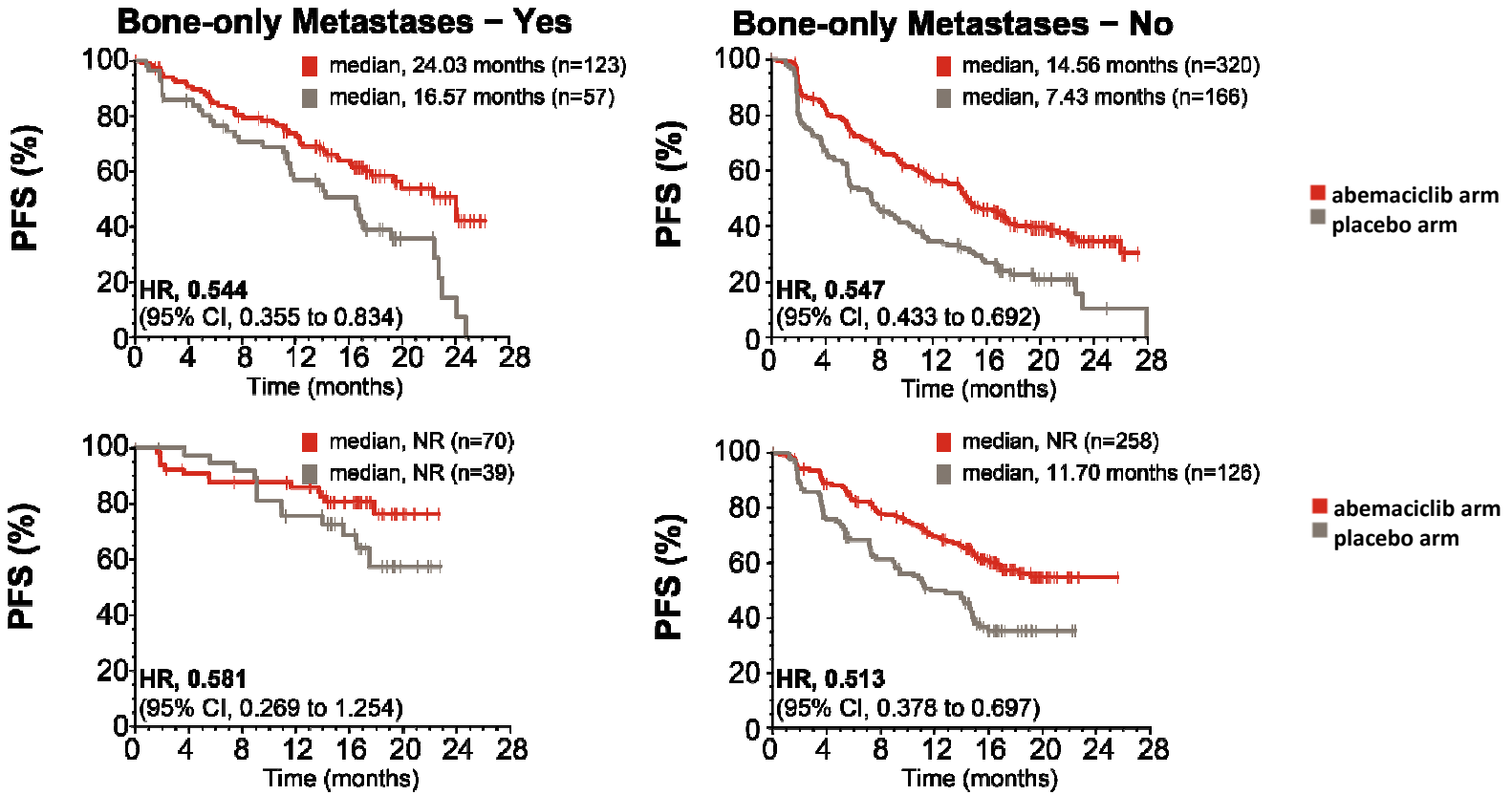
MONARCH 2/3 Subgroup Analysis by Bone only

MONARCH 2

Abema + Ful
(MBC 2L)

MONARCH 3

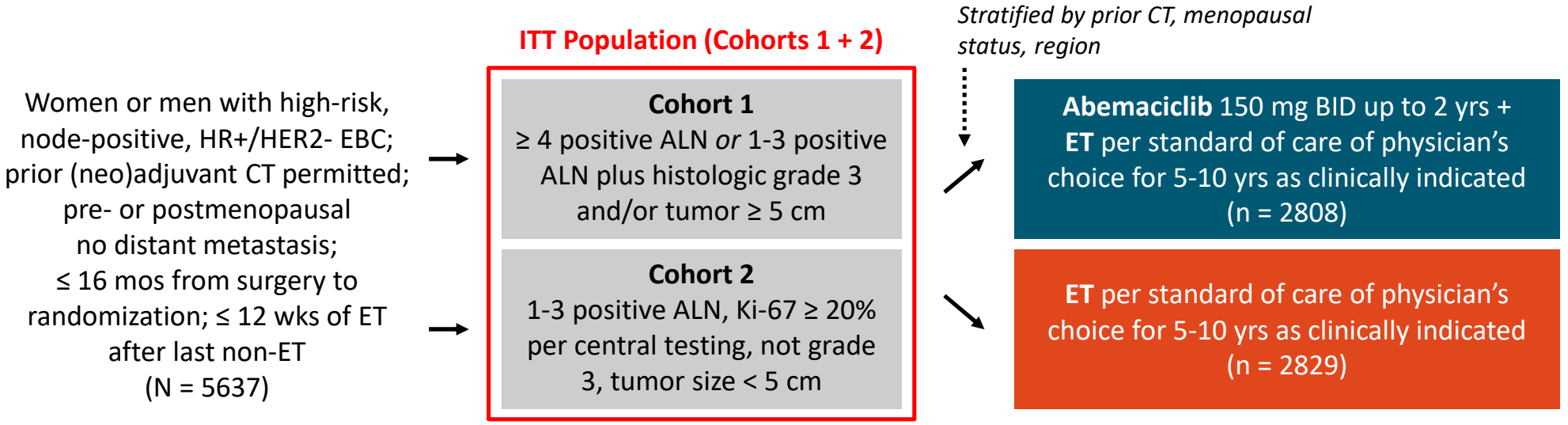
Abema + NSAI
(MBC 1L)



O'Shaughnessy J, et al. *Cancer Res* 2018;78(suppl 13):Abstract CT099.

monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

- International, randomized, open-label phase III trial



- Primary endpoint: iDFS
  - Planned for after ~ 390 iDFS events (~ 85% power, assumed iDFS HR of 0.73, cumulative 2-sided α = 0.05)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki-67 high (≥ 20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

Slide credit: clinicaloptions.com

monarchE: Baseline Characteristics

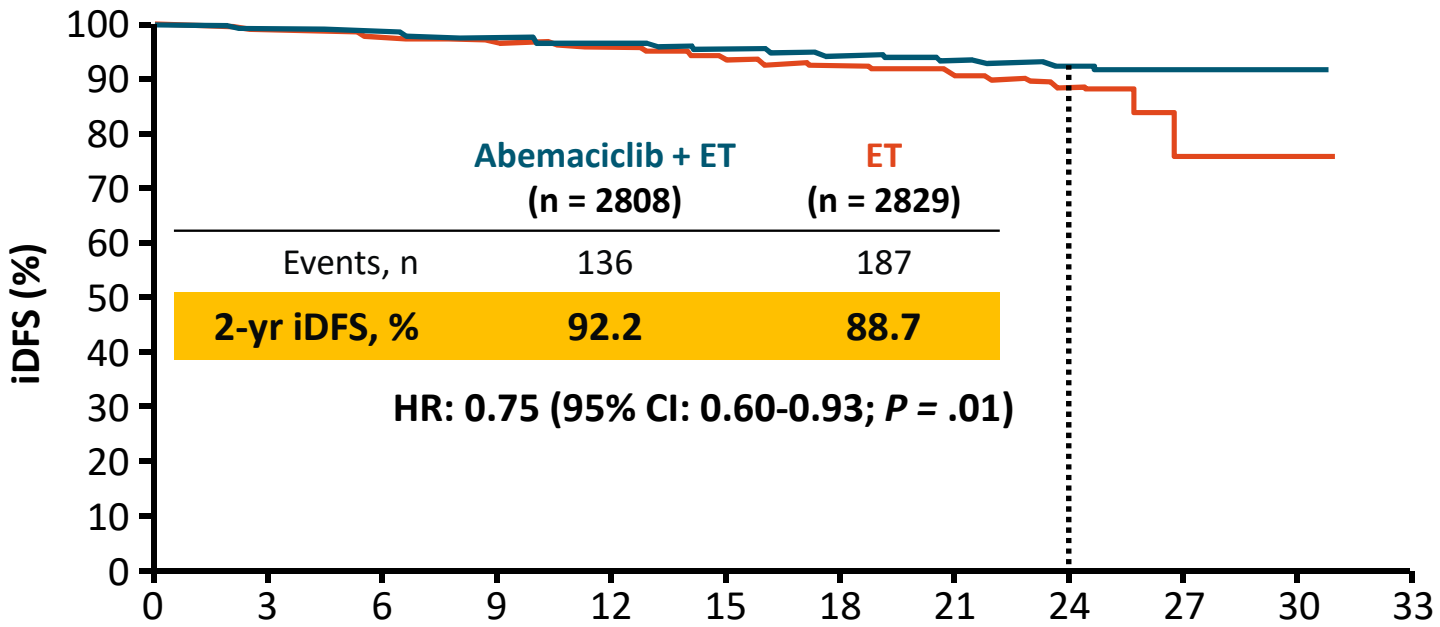
Characteristic	Abemaciclib + ET (n = 2808)	ET Alone (n = 2829)
Median age, yrs (range)	51 (23-89)	51 (22-86)
▪ < 65	84.4	85.4
▪ ≥ 65	15.6	14.6
North America and Europe/Asia/other, %	52.4/20.4/27.2	52.3/20.6/27.1
Pre/postmenopausal, %	43.5/56.5	43.5/56.5
Prior CT, %		
▪ Neoadjuvant	37.0	37.0
▪ Adjuvant	58.5	58.2
▪ None	4.5	4.7
Prior neoadjuvant/ adjuvant RT, %	2.5/93.3	2.9/92.9
Positive axillary LN, %		
▪ 0	0.2	0.2
▪ 1-3	39.9	40.4
▪ ≥ 4	59.8	59.3
ER/PgR positive, %	99.1/86.2	99.2/86.7

Characteristic, %	Abemaciclib + ET (n = 2808)	ET Alone (n = 2829)
Pathologic tumor size		
▪ < 2 cm	27.8	27.0
▪ 2-5 cm	48.8	50.2
▪ ≥ 5 cm	21.7	21.6
Histologic grade at diagnosis		
▪ 1	7.4	7.6
▪ 2	48.9	49.3
▪ 3	38.8	37.7
▪ Not assessed	4.5	4.9
Ki-67 index < 20/≥ 20	33.9/44.9	34.4/43.6
TNM stage (derived)		
▪ IA	0.1	0
▪ IIA	11.5	12.5
▪ IIB	13.9	13.7
▪ IIIA	36.6	36.2
▪ IIIB	3.7	3.2
▪ IIIC	33.8	34.0

Johnston. JCO. 2020;38:3987.

Slide credit: clinicaloptions.com

monarchE: iDFS (Primary Endpoint)



Patients at Risk, n												
Abe + ET	2808	2676	2613	2543	1996	1371	918	566	245	3	1	0
ET	2829	2699	2649	2562	2013	1405	932	586	262	7	6	0

- Patients with Ki-67 high tumors also experienced significant iDFS improvement with abemaciclib + ET vs ET alone
  - HR: 0.70 (95% CI: 0.52-0.92; *P* = .01)

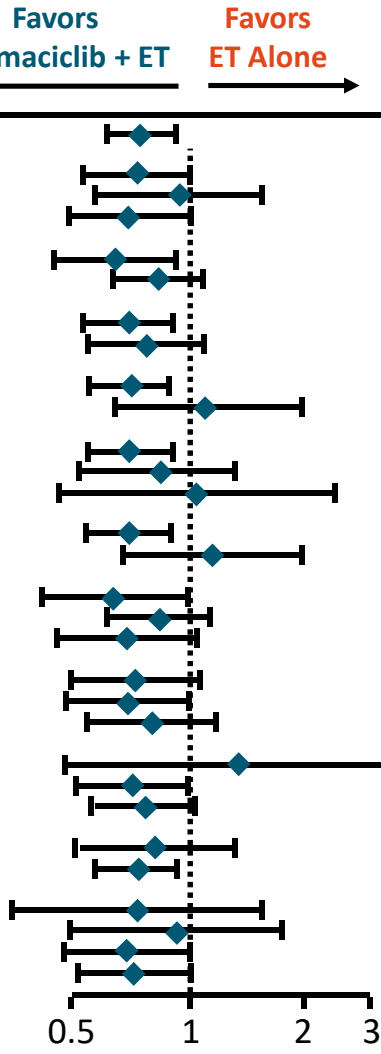
Median f/u: 19.1 mos in both arms. Curves should not be interpreted beyond 24 mos due to limited f/u.

Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

Slide credit: clinicaloptions.com

monarchE: iDFS by Subgroup

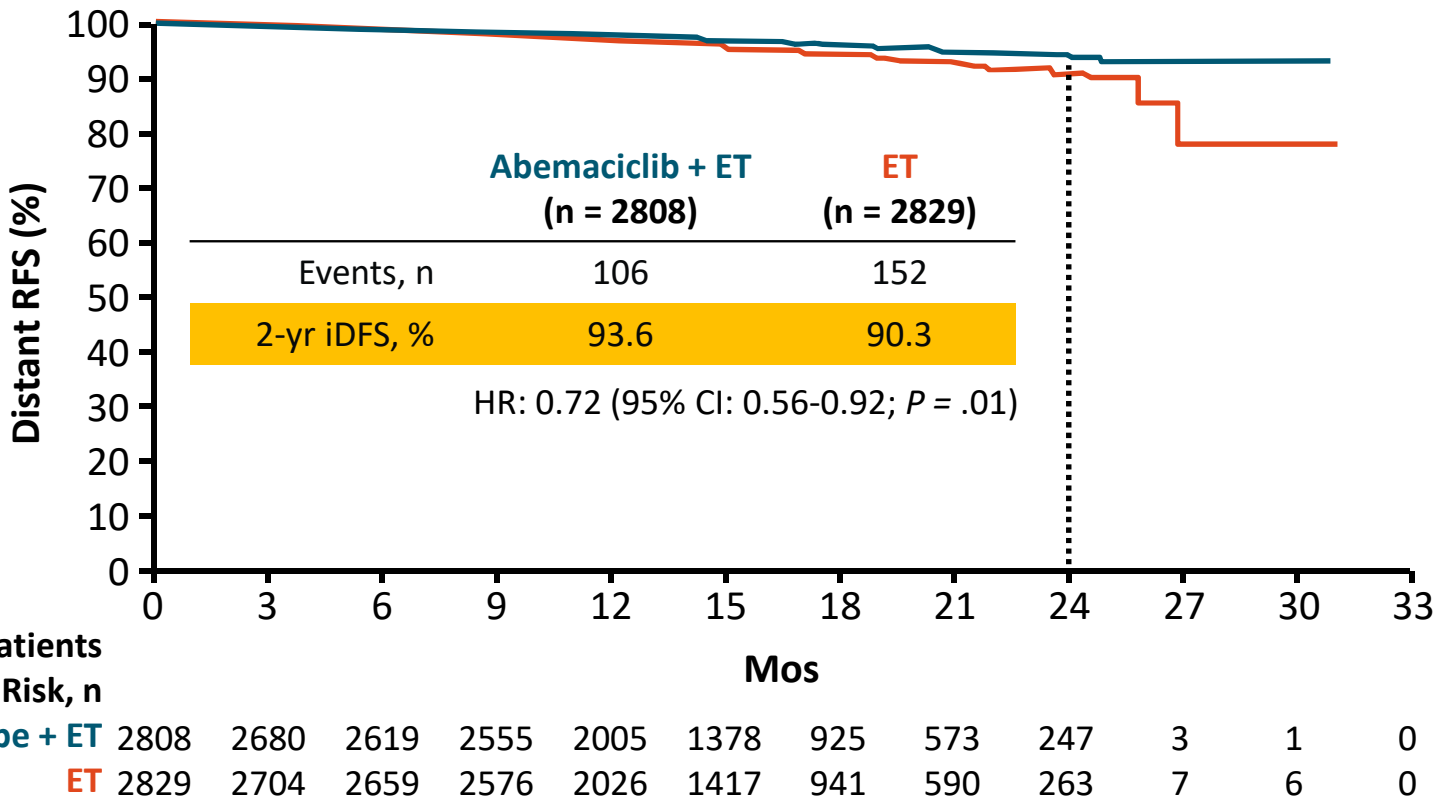
Subgroup Analyzed		Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	HR (95% CI)
Overall		2808	136	2829	187	0.75 (0.60-0.93)
Region	North America/Europe	1470	62	1479	89	0.72 (0.52-1.00)
	Asia	574	28	582	30	0.93 (0.55-1.55)
	Other	764	46	768	68	0.69 (0.48-1.00)
Menopausal status	Premenopausal	1221	46	1232	72	0.63 (0.44-0.92)
	Postmenopausal	1587	90	1597	115	0.82 (0.62-1.08)
Prior chemotherapy	Neoadjuvant	1039	76	1048	111	0.69 (0.52-0.93)
	Adjuvant	1642	52	1647	69	0.77 (0.54-1.10)
Age, yrs	< 65	2371	111	2416	164	0.69 (0.54-0.88)
	≥ 65	437	25	413	23	1.11 (0.63-1.96)
Race	White	1947	93	1978	138	0.69 (0.53-0.90)
	Asian	675	31	669	37	0.82 (0.51-1.33)
	All others	146	11	140	11	1.04 (0.45-2.40)
Baseline ECOG PS	0	2405	110	2369	159	0.69 (0.54-0.88)
	1	401	26	455	27	1.14 (0.66-1.95)
Primary tumor size, cm	< 2	780	31	765	48	0.63 (0.40-0.99)
	2-5	1369	67	1419	86	0.83 (0.60-1.14)
	≥ 5	610	35	612	52	0.68 (0.44-1.04)
No. of positive lymph nodes	1-3	1119	42	1143	60	0.71 (0.48-1.06)
	4-9	1105	47	1125	72	0.69 (0.48-0.99)
	10	575	45	554	55	0.79 (0.53-1.17)
Histologic grade	G1	209	8	215	6	1.35 (0.47-3.89)
	G2	1373	55	1395	81	0.71 (0.50-0.99)
	G3	1090	67	1066	88	0.76 (0.55-1.04)
Progesterone receptor	Negative	298	30	294	38	0.81 (0.50-1.30)
	Positive	2421	104	2453	146	0.73 (0.57-0.94)
Tumor stage	IIA	323	11	353	16	0.73 (0.34-1.57)
	IIB	389	17	387	19	0.92 (0.48-1.78)
	IIIA	1027	41	1024	61	0.68 (0.46-1.02)
	IIIC	950	59	962	84	0.71 (0.51-0.99)



Johnston. JCO. 2020;38:3987.

Slide credit: clinicaloptions.com

monarchE: Distant RFS



- Most iDFS events were distant recurrences (87 with abemaciclib + ET vs 138 with ET alone)
- Common sites of distant recurrence were bone, liver, and lung
- Distant RFS benefit consistent across subgroups

Median f/u: 19.1 mos in both arms. Curves should not be interpreted beyond 24 mos due to limited f/u.

Johnston. JCO. 2020;38:3987.

Slide credit: clinicaloptions.com

monarchE: Treatment-Emergent AEs

Treatment-Emergent AE, n (%)	Abemaciclib + ET (n = 2791)			ET (n = 2800)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	**2731 (97.9)**	**1200 (43.0)**	**70 (2.5)**	**2410 (86.1)**	**335 (12.0)**	**19 (0.7)**
▪ Diarrhea	2294 (82.2)	212 (7.6)	0	199 (7.1)	3 (0.1)	0
▪ Neutropenia	1246 (44.6)	501 (18.0)	18 (0.6)	141 (5.0)	16 (0.6)	3 (0.1)
▪ Fatigue	1073 (38.4)	78 (2.8)	0	433 (15.5)	4 (0.1)	0
▪ Leukopenia	1027 (36.8)	301 (10.8)	4 (0.1)	171 (6.1)	10 (0.4)	0
▪ Abdominal pain	948 (34.0)	37 (1.3)	0	227 (8.1)	9 (0.3)	0
▪ Nausea	779 (27.9)	13 (0.5)	0	223 (8.0)	1 (0)	0
▪ Anemia	638 (22.9)	47 (1.7)	1 (0)	90 (3.2)	9 (0.3)	1 (0)
▪ Arthralgia	571 (20.5)	6 (0.2)	0	876 (31.3)	18 (0.6)	0
▪ Hot flush	393 (14.1)	3 (0.1)	0	587 (21.0)	8 (0.3)	0
▪ Lymphopenia	372 (13.3)	140 (5.0)	2 (0.1)	94 (3.4)	13 (0.5)	0
▪ Thrombocytopenia	341 (12.2)	25 (0.9)	6 (0.2)	40 (1.4)	1 (0)	2 (0.1)
▪ Vomiting	455 (16.3)	13 (0.5)	0	117 (4.2)	2 (0.1)	0
▪ Headache	482 (17.3)	6 (0.2)	0	359 (12.8)	3 (0.1)	0
▪ Decreased appetite	312 (11.2)	15 (0.5)	0	54 (1.9)	1 (0)	0

Johnston. JCO. 2020;38:3987.

monarchE: Treatment-Emergent AEs of Special Interest

Treatment-Emergent AE, n (%)	Abemaciclib + ET (n = 2791)			ET (n = 2800)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
AST increase	257 (9.2)	43 (1.5)	3 (0.1)	106 (3.8)	13 (0.5)	0
ALT increase	265 (9.5)	59 (2.1)	5 (0.2)	119 (4.3)	16 (0.6)	0
Alopecia	254 (9.1)	0	0	53 (1.9)	0	0
Venous thromboembolic event	63 (2.3)	27 (1.0)	6 (0.2)	14 (0.5)	4 (0.1)	0
Interstitial lung disease	75 (2.7)	9 (0.3)	0	33 (1.2)	1 (0)	0

- 14 patients (0.5%) died in each arm while on study treatment or within 30 days of discontinuation
  - 11 patients in abemaciclib arm died due to AEs, 2 of which (diarrhea and pneumonitis) were considered related to study treatment by investigator
  - 7 patients in control arm died due to AEs

Johnston. JCO. 2020;38:3987.

Slide credit: clinicaloptions.com

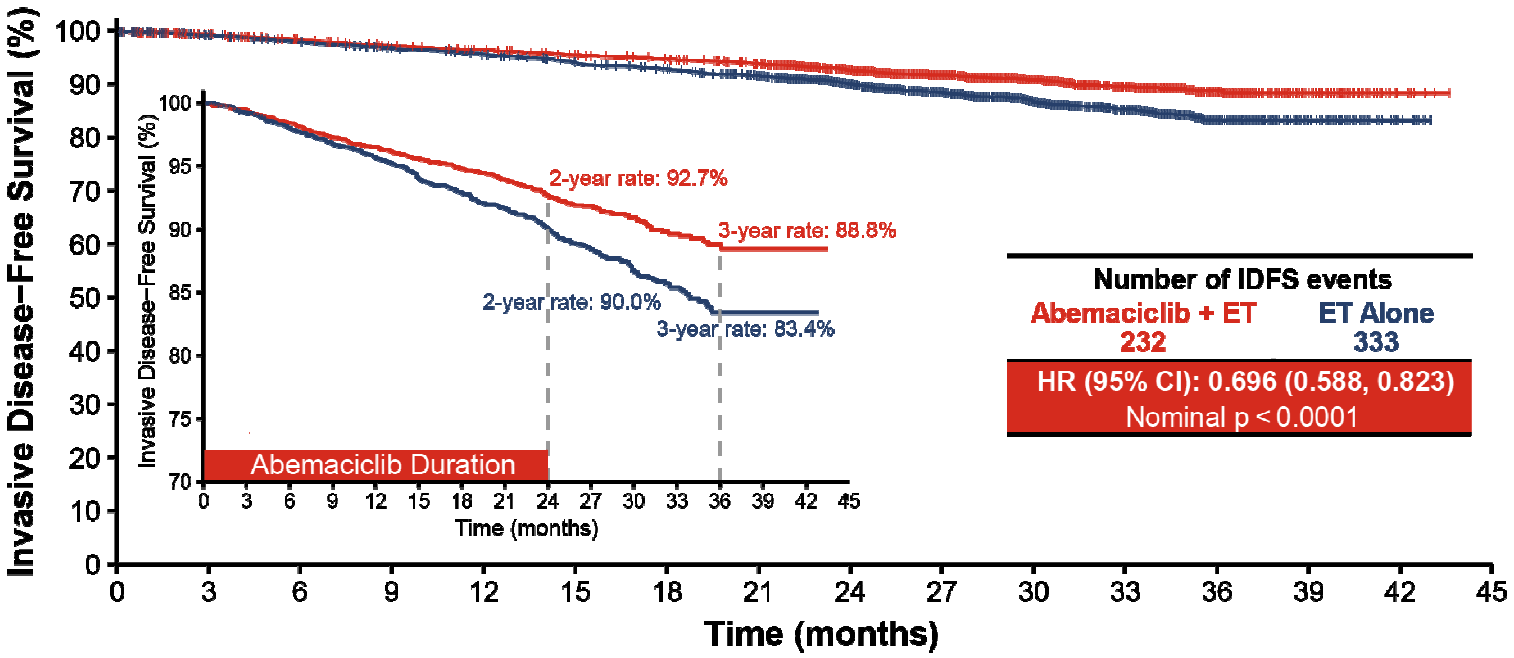
Description of Analysis Timepoints (2021 ASCO update)

Analysis Timepoints	Interim Analysis[a,1-2]	Primary Outcome[3]	Additional Follow-up 1 (AFU1)
Date	16 March 2020	08 July 2020	01 April 2021
Median Follow-up (months)	15.5	19.1	27.1
IDFS Events	323	395	565
Off Study Treatment	26.4%	41.0%	89.6%
Completed 2-year Treatment Period	12.5%	25.5%	72.2%

[a]statistically significant improvement in IDFS in ITT population declared at this timepoint
[1]Johnston SRD, et al. J Clin Oncol. 2020;38(34):3987-3998; [2]Johnston SD et al ESMO 2020; [3]Rastogi P et al SABCS 2020

- Methods, statistical considerations previously disclosed
- Key AFU1 analyses: IDFS and DRFS in both ITT and prespecified Ki-67 populations; piecewise HR estimates within each year for IDFS and DRFS in the ITT population (exploratory)
- The study will continue to final OS analysis

IDFS Benefit Maintained with Additional Follow-up in ITT population

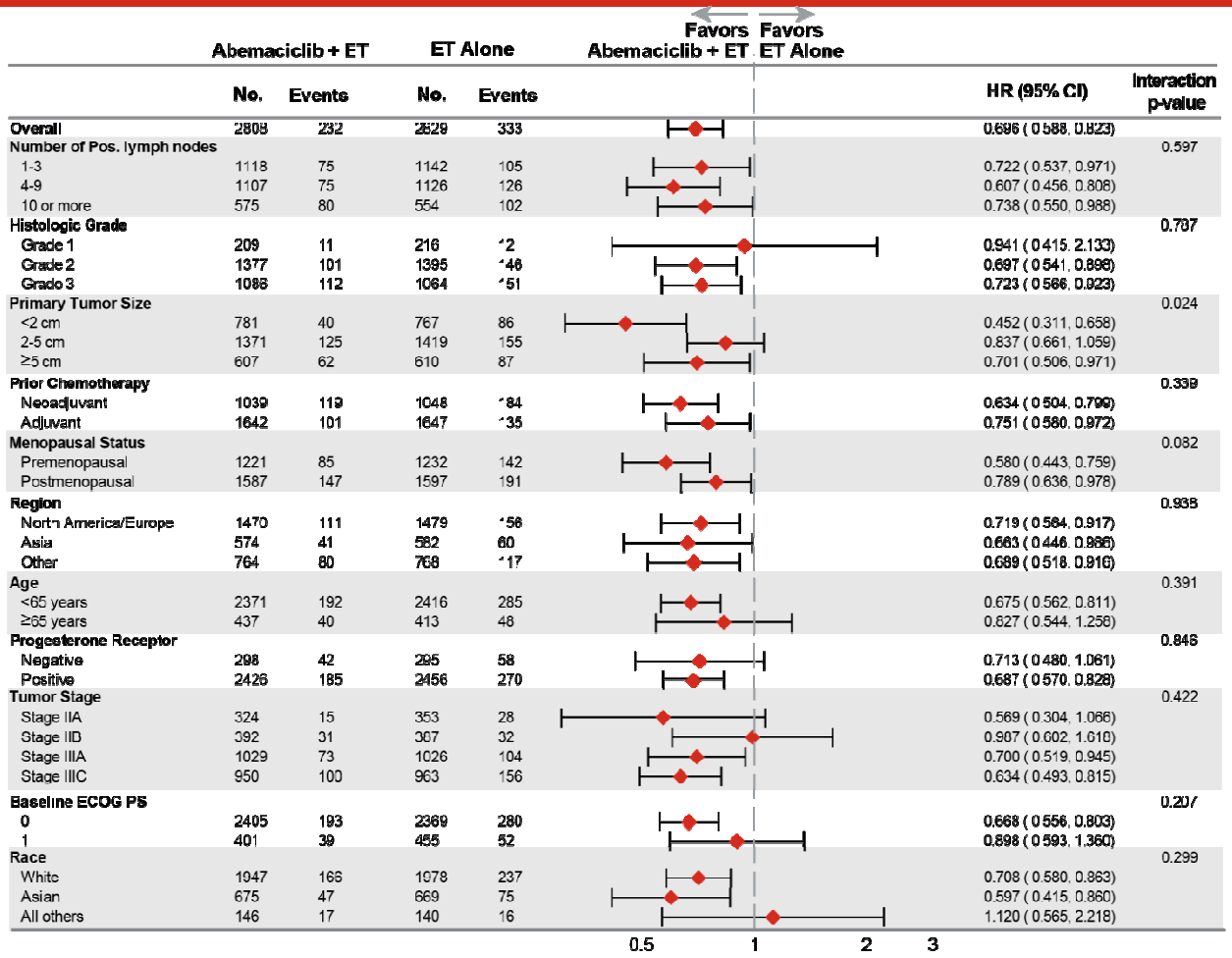


Number at risk																
Abemaciclib + ET	2808	2680	2621	2579	2547	2508	2477	2430	1970	1287	919	522	275	67	8	0
ET Alone	2829	2700	2652	2608	2572	2513	2472	2400	1930	1261	906	528	281	64	10	0

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.

Joyce O'Shaughnessy

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	80	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, 1.256)	
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	0.907 (0.602, 1.610)	
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)	

Joyce O'Shaughnessy

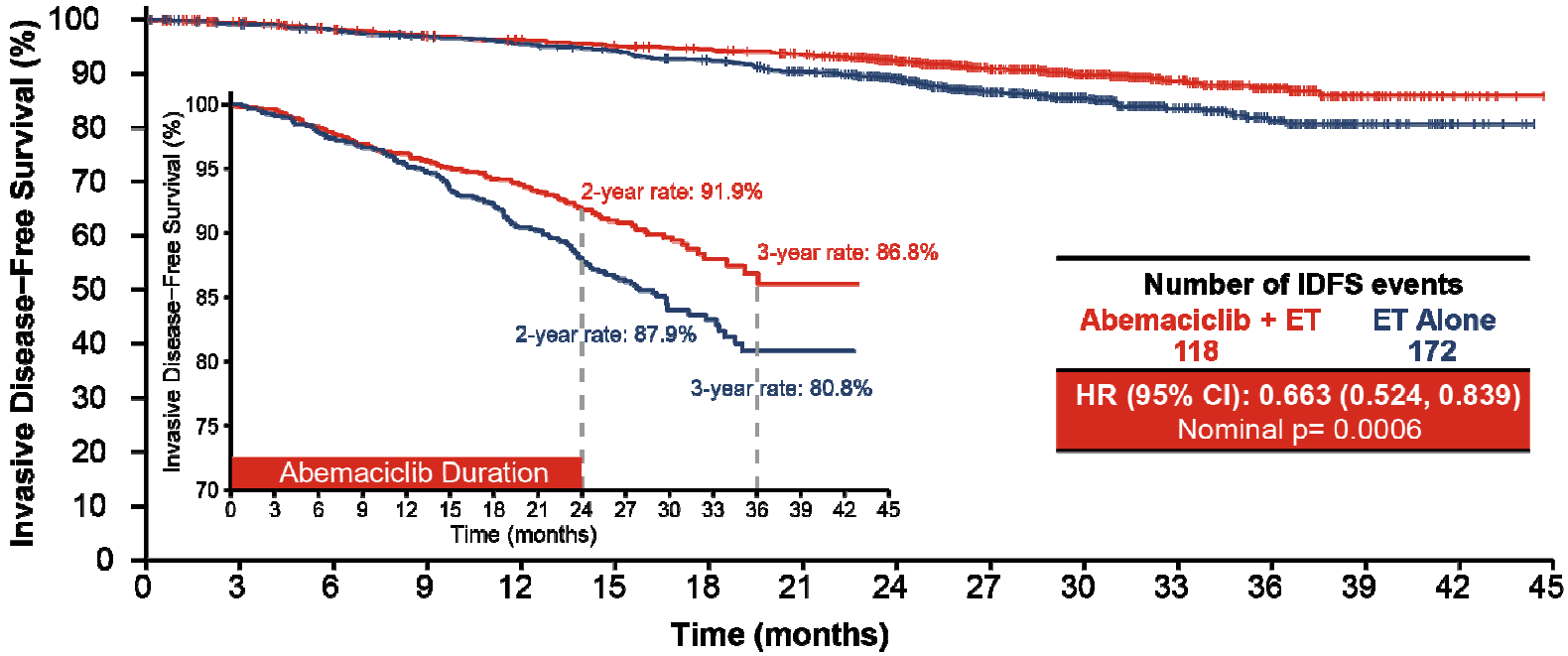
Abemaciclib Treatment Effect Over Time

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

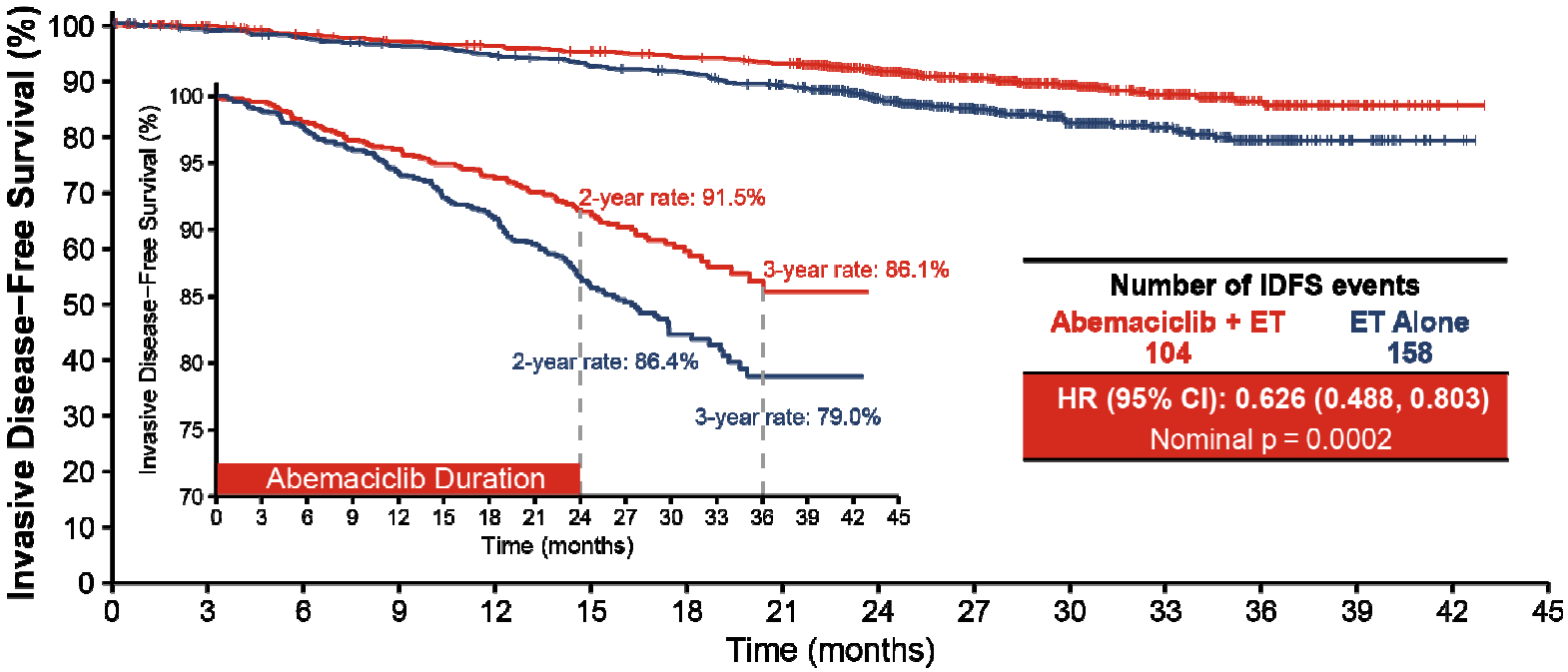


Number at risk																
Abemaciclib + ET	1262	1221	1189	1167	1155	1139	1123	1094	870	546	377	203	109	25	2	0
ET Alone	1236	1197	1177	1158	1142	1114	1096	1041	827	520	367	198	107	25	3	0

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.

Joyce O'Shaughnessy

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.

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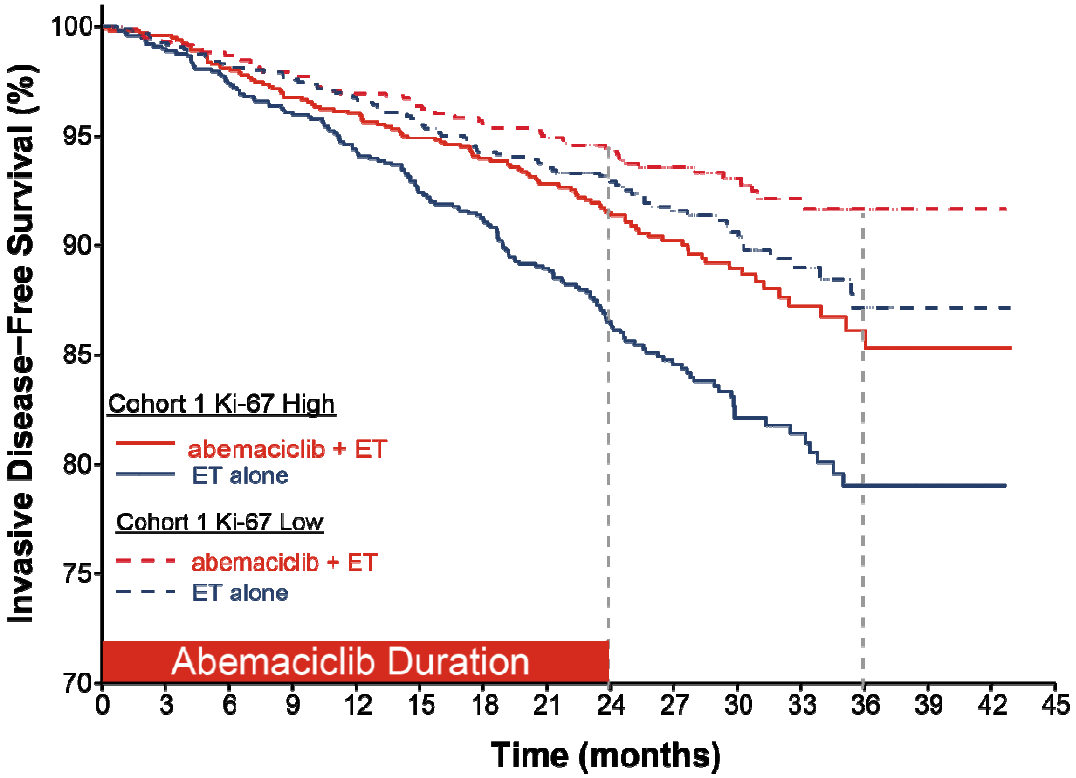
Ki-67 as a prognostic marker in Cohort 1



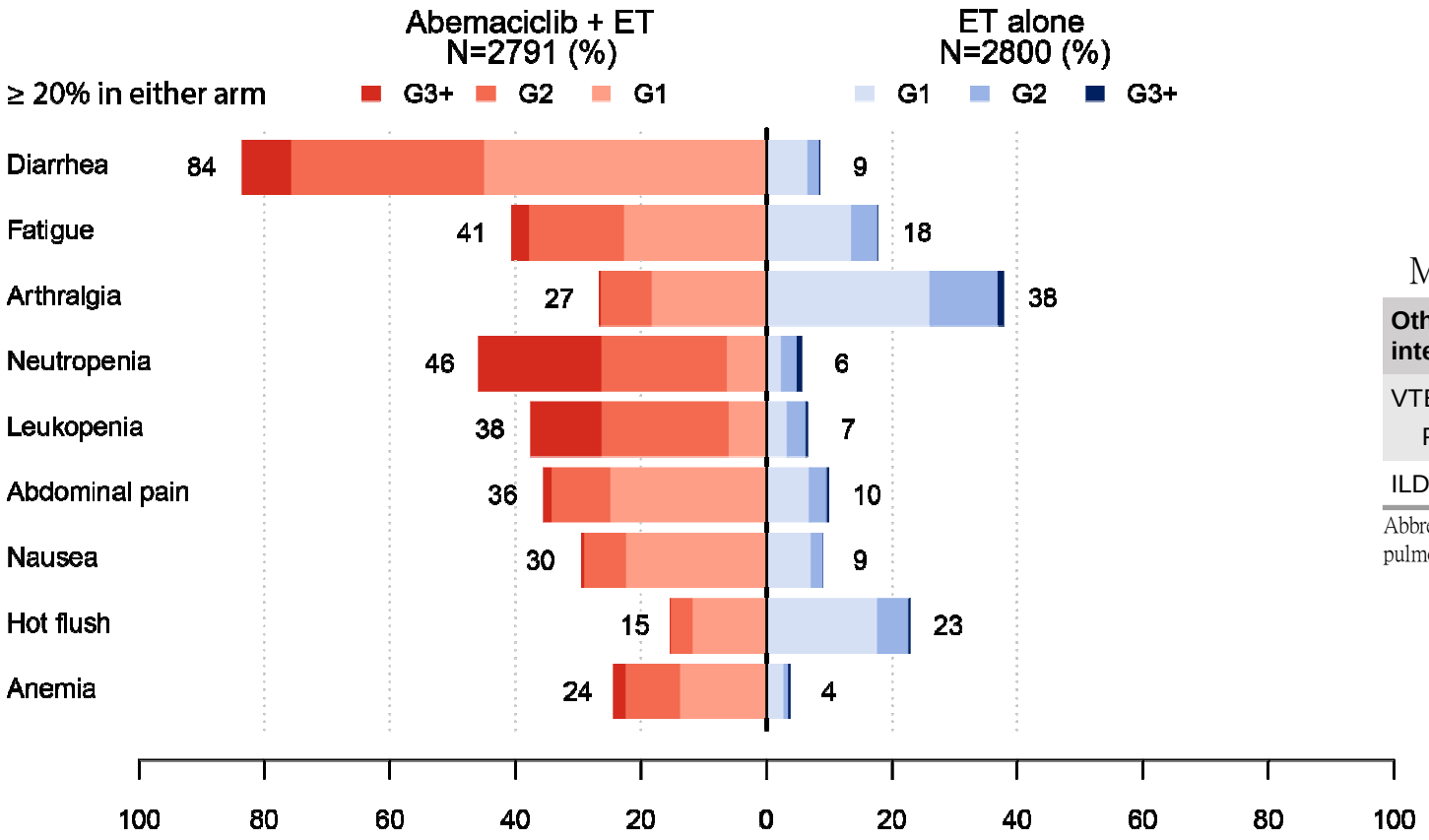
	Abemaciclib + ET	ET alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	966	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

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



Median duration of abemaciclib: 23.7

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

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

Joyce O'Shaughnessy

What you should know about Abemaciclib

- Abemaciclib is indicated for:
  - High risk HR(+) EBC; adjuvant 2 years Abemaciclib + ET
  - All lines of MBC treatment

- Bone only MBC 1L: cost-effectiveness based on Taiwan NHI system

- Rapid onset of efficacy, manageable diarrhea by prevention, less myelosuppressive.

Thank you !