
بسم الله الرحمن الرحيم

20th Congress of Iranian Society of Medical Oncology & Hematology

بیستمین کنگره سراسری انجمن هماتولوژی و انکولوژی پزشکی ایران (سال ۱۴۰۰)

Adjuvant Therapy for Patients With HR+/HER2- EBC at High Risk of Recurrence

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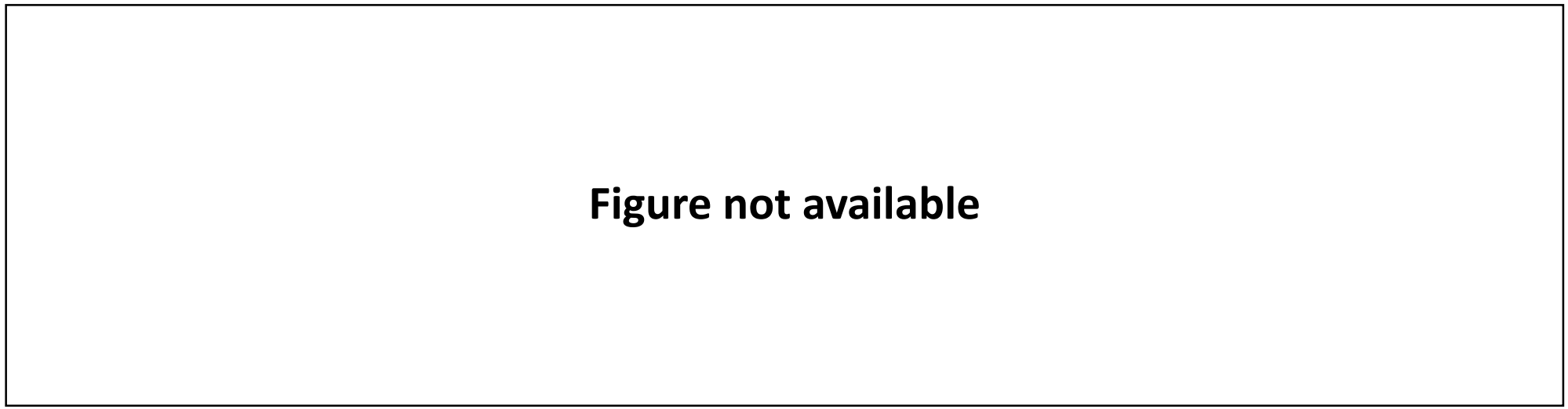
Selective CDK4/6 Inhibitors

IC_{50}	Palbociclib	Ribociclib	Abemaciclib
CDK4	9–11 nM	10 nM	2 nM
CDK6	15 nM	39 nM	5 nM
CDK2	>10 µM	>50 µM	>500 nM
CDK9	ND	ND	57 nM



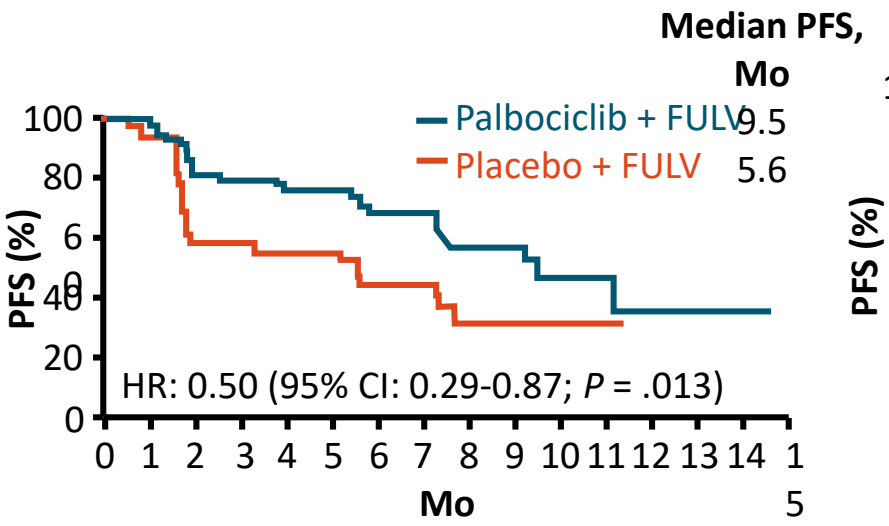
Chen. Mol Cancer Ther. 2016;15:2273. Ashgar. Nat Rev Drug Discov. 2015;14:130. Poratti. Eur J Med Chem. 2019;172:143.

Slide credit: clinicaloptions.com

CDK4/6i Is Active in Premenopausal Patients With MBC, Regardless of Endocrine Therapy Partner

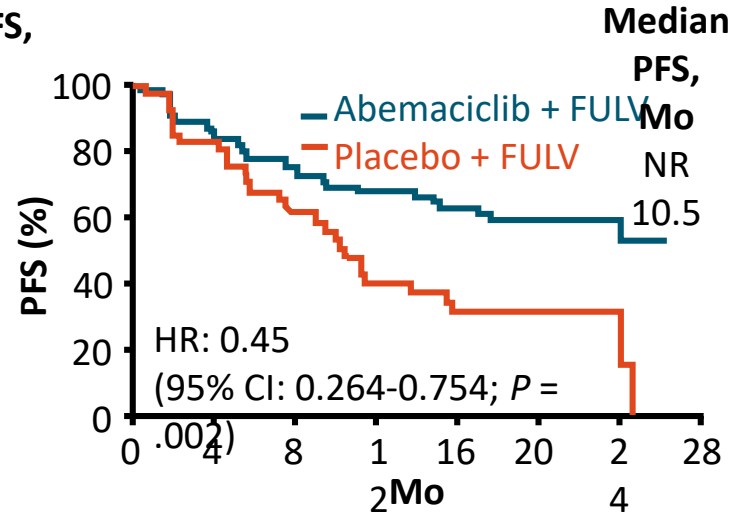
PALOMA-3[1]

- N = 108
- FULV + goserelin
- Hazard ratio: 0.50; *P* = .013



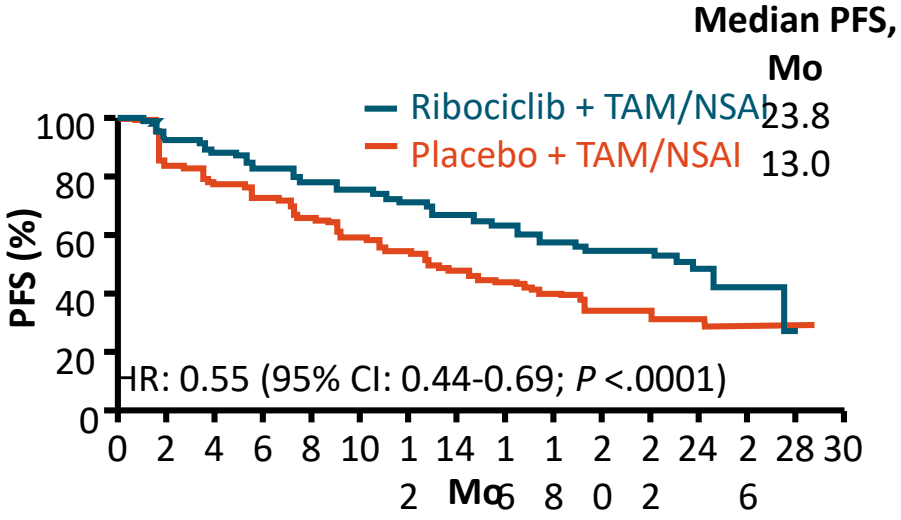
MONARCH-2[2]

- N = 114
- FULV + GnRH
- Hazard ratio: 0.45; *P* = .002



MONALEESA-7[3]

- N = 672
- TAM* or NSAI+ goserelin
- Hazard ratio: 0.55; *P* = 1 x 10^{-9}



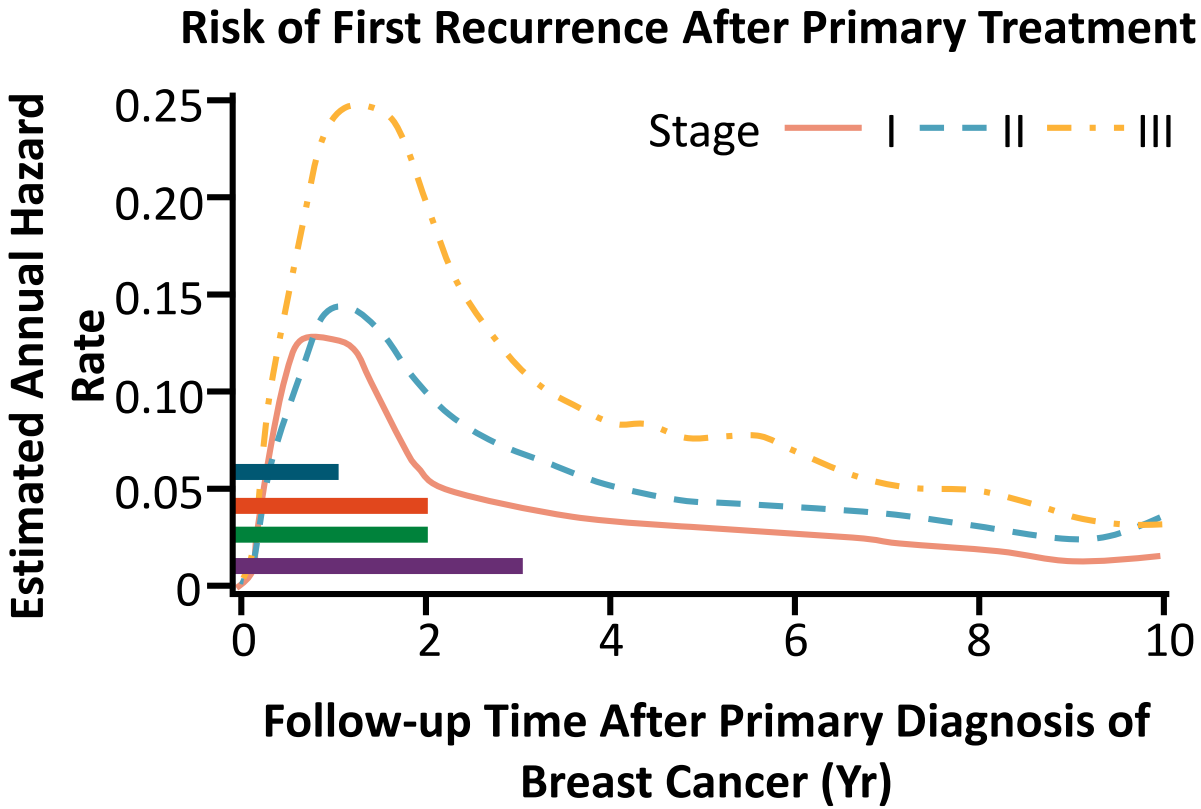
- **Ribociclib is currently the only CDK4/6i FDA approved in the first-line setting in MBC for pre/perimenopausal women[4-6]**

*TAM should not be given with ribociclib due to concerns about QT prolongation.[4]

1. Loibl. Oncologist. 2017;22:10283. 2. Neven. ASCO 2018. Abstr 1002. 3. Tripathy. Lancet Oncol. 2018;19:904.
4. Ribociclib PI. 5. Abemaciclib PI. 6. Palbociclib PI.

Slide credit: clinicaloptions.com

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



PENELOPE-B
palbociclib
After neoadjuvant, high risk

monarchE
abemaciclib
High-risk CPR factors, Ki-67

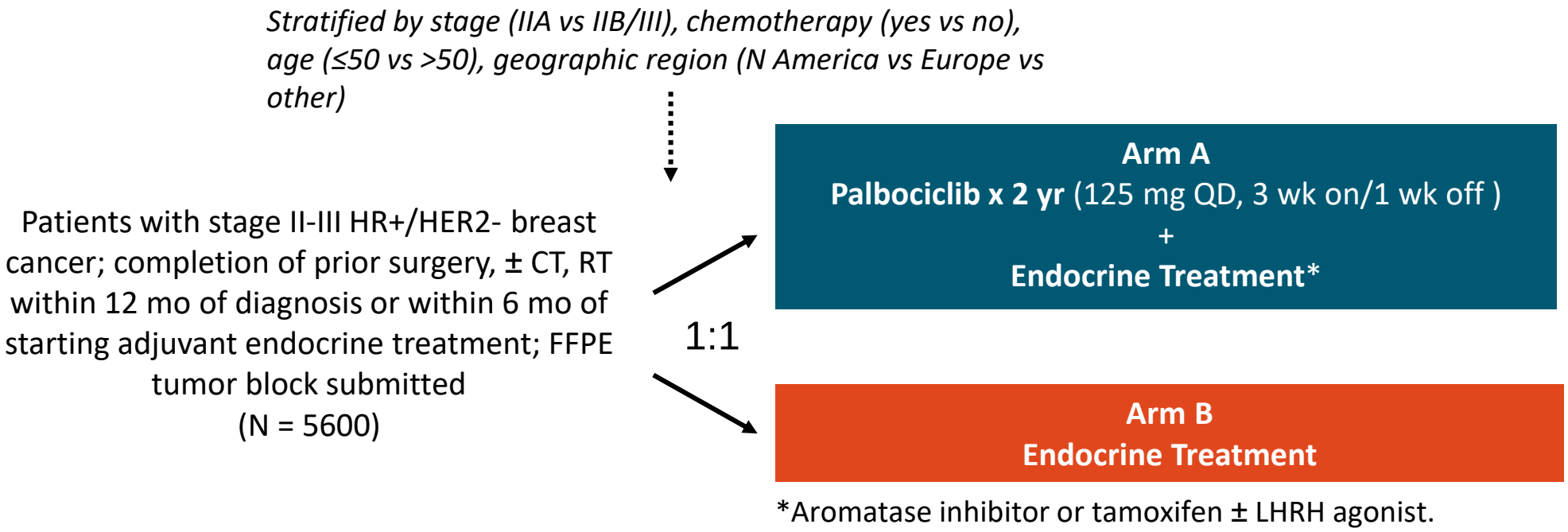
PALLAS
palbociclib
Stage II, III

NATALEE
ribociclib
Stage II, III

Cheng. Cancer Epidemiol Biomarkers Prev. 2012; 21:800.

Slide credit: clinicaloptions.com

PALLAS: Phase III Open-Label Study of Palbociclib and Adjuvant Endocrine Therapy



- Primary endpoint: invasive disease-free survival

Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021; 22:212.

Slide credit: clinicaloptions.com

PALLAS: Patient Characteristics (ITT)

Variable	Palbociclib + ET (n = 2883)	ET (n = 2877)
Median age, yr (range)	52 (25-90)	52 (22-85)
Stage, n (%)		
▪ IIA	504 (17.5)	509 (17.7)
▪ IIB	968 (33.6)	951 (33.1)
▪ III	1402 (25.0)	1408 (48.9)
T-stage, n (%)		
▪ 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, n (%)		
▪ 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)

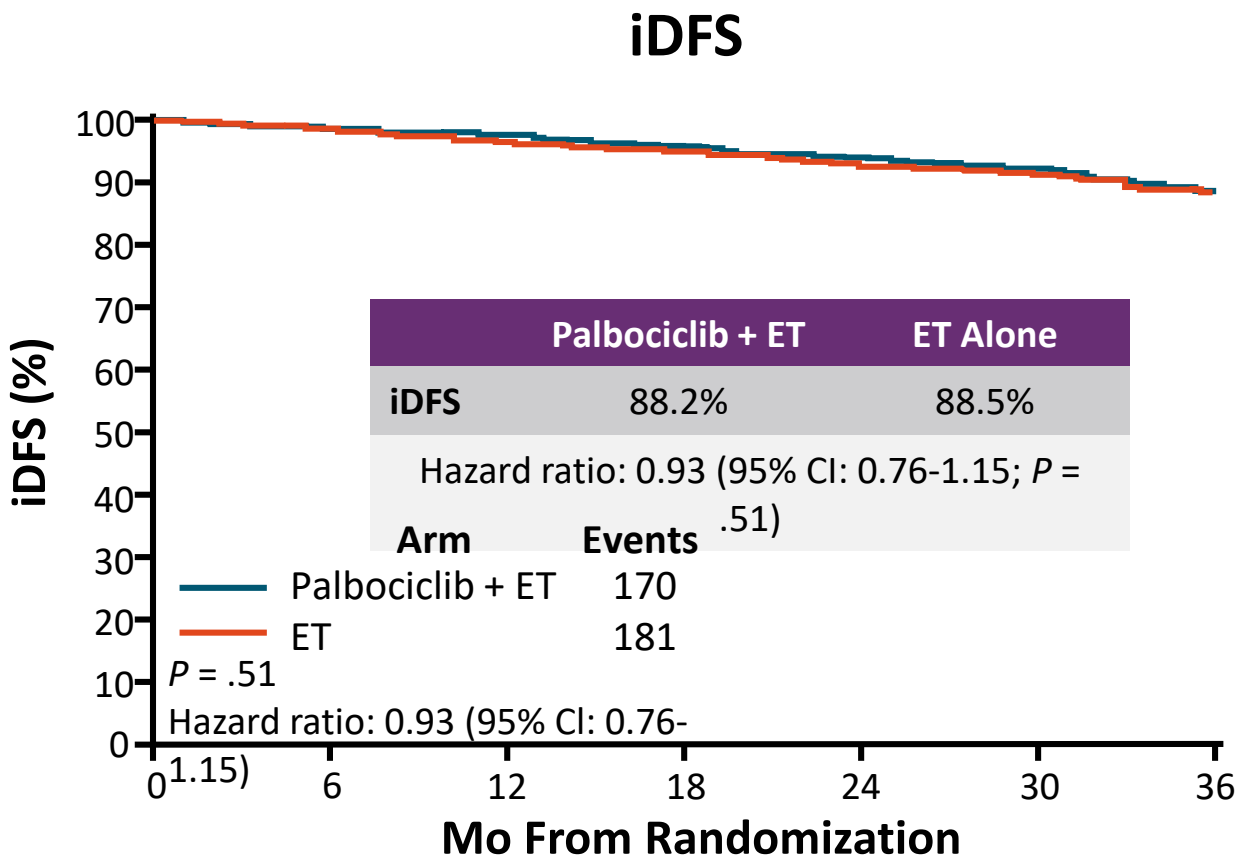
Variable, n (%)	Palbociclib + ET (n = 2883)	ET (n = 2877)
Histologic grade		
▪ 1	300 (10.4)	313 (10.9)
▪ 2	1622 (56.3)	1658 (57.6)
▪ 3	836 (29.0)	767 (26.7)
Prior chemotherapy	2384 (82.7)	2370 (82.4)
Initial adjuvant ET		
▪ Aromatase inhibitor	1954 (67.8)	1918 (66.7)
▪ Tamoxifen	923 (32.0)	949 (33.0)
Concurrent adjuvant LHRH agonist	532 (18.5)	604 (21.1)

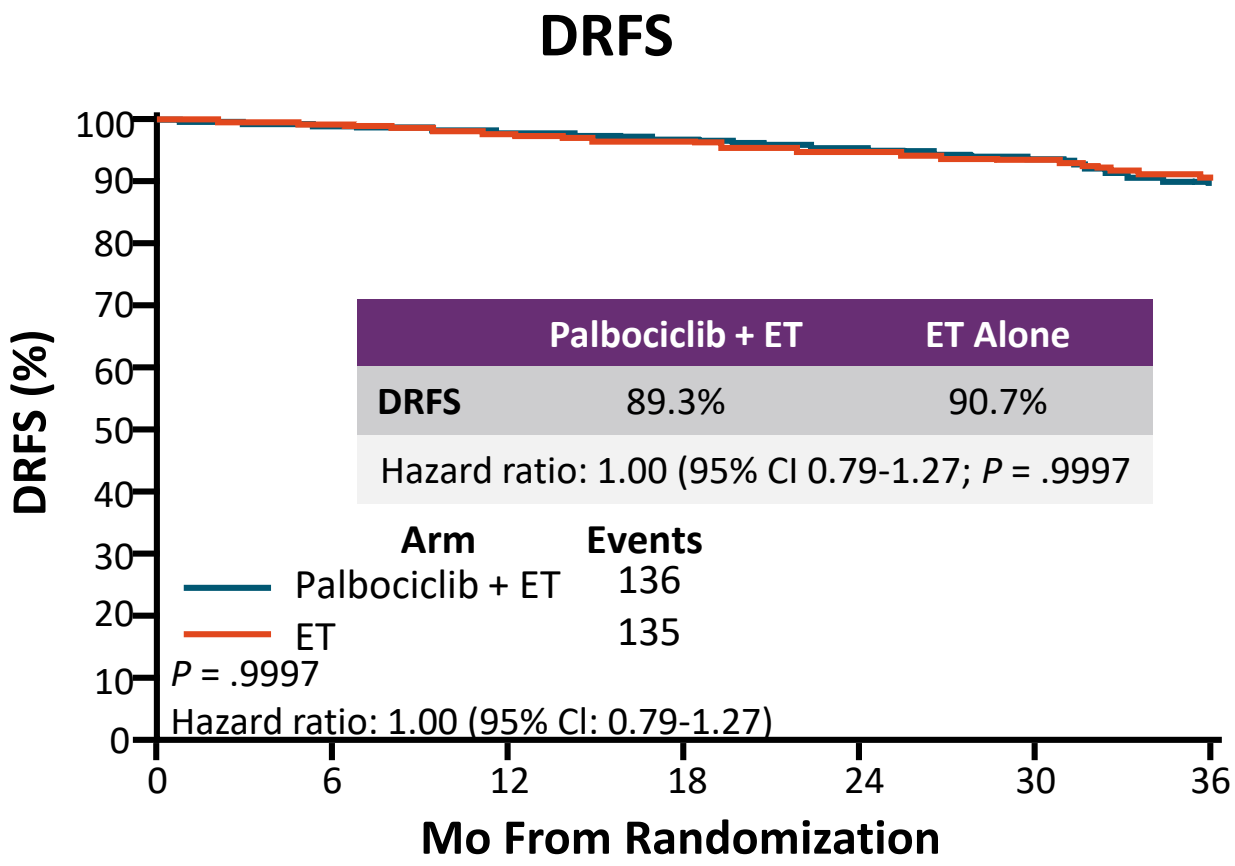
- 5760 patients were randomized and included in the ITT population (from 9/2015 to 11/2018)
- Majority had higher-stage disease and had received prior chemotherapy
- 58.7% had high clinical risk disease, described as:
  - ≥4 nodes involved (≥N2), or 1-3 nodes with either T3/T4 and/or grade 3 disease

Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021; 22:212.

Slide credit: clinicaloptions.com

PALLAS: Primary Endpoint iDFS

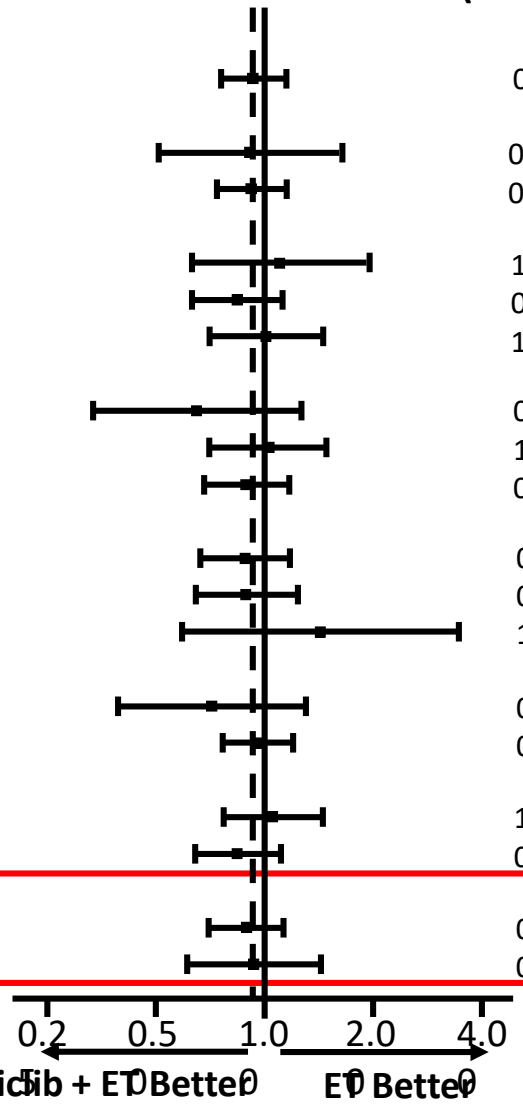




- At a median follow-up of 23.7 mo, no significant difference in either 3-yr iDFS or DRFS was observed

PALLAS: Subgroup Analysis

Subgroup	Palbociclib + ET *Events/N*	ET *Events/N*	Hazard Ratio (95% CI)	*P* Value for Interaction
All Patients	170/2883	181/2877	0.93 (0.75-1.14)	
Stage				.99
IIA	21/504	25/509	0.91 (0.51-1.63)	
IIB/III	149/2370	156/2359	0.92 (0.73-1.15)	
T-Stage				.60
T0/T1/Tis/TX	26/557	22/500	1.10 (0.62-1.94)	
T2	84/1603	101/1636	0.84 (0.63-1.12)	
T3/T4	60/722	58/741	1.01 (0.70-1.44)	
N-Stage				.50
N0	14/367	23/383	0.65 (0.33-1.26)	
N1	53/1427	53/1415	1.02 (0.70-1.50)	
N2/N3	103/1088	105/1079	0.89 (0.68-1.17)	
Histologic Grade				.56
1/2	86/1922	100/1971	0.88 (0.66-1.18)	
3	73/836	72/767	0.89 (0.65-1.24)	
X	11/122	9/139	1.43 (0.59-3.44)	
Neo/Adjuvant Chemotherapy				.36
No	18/498	27/507	0.71 (0.39-1.28)	
Yes	152/2384	154/2370	0.96 (0.77-1.20)	
Age Group				.29
≤50 yr	79/1309	73/1304	1.06 (0.77-1.45)	
>50 yr	91/1573	108/1573	0.84 (0.64-1.11)	
Clinical Risk				.87
High risk	131/1710	136/1672	0.89 (0.70-1.13)	
Low risk	39/1172	45/1205	0.93 (0.61-1.43)	



Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021; 22:212.

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PALLAS: Palbociclib Discontinuation and Exposure

Palbociclib Discontinuations

2840 patients were randomized to Arm A (ITT); at data cutoff 1/2020:

- 32% had completed 2 yr
- 26% were still receiving palbociclib
- **42% had discontinued prematurely**

27% of Arm A (770 of 2840) discontinued due to AEs:

- Neutropenia (461, 16%)
- Fatigue (71, 3%)

Arm A Patient Status	Palbociclib + ET
Initiated palbociclib	2840
Ongoing palbociclib at cutoff, n (%)	725 (25.5)
Completed palbociclib per protocol, n (%)	916 (32.3)
Early discontinuation of palbociclib, n (%)	1199 (42.2)
▪ AE* (including unacceptable toxicity)	770 (27.1)
▪ Patient noncompliance/nonadherence	128 (4.5)
▪ Development of recurrent disease/second malignancy	104 (3.7)
▪ Informed consent withdrawal	100 (3.5)
▪ Other reasons	97 (3.4)

*Most common AEs were neutropenia and fatigue.

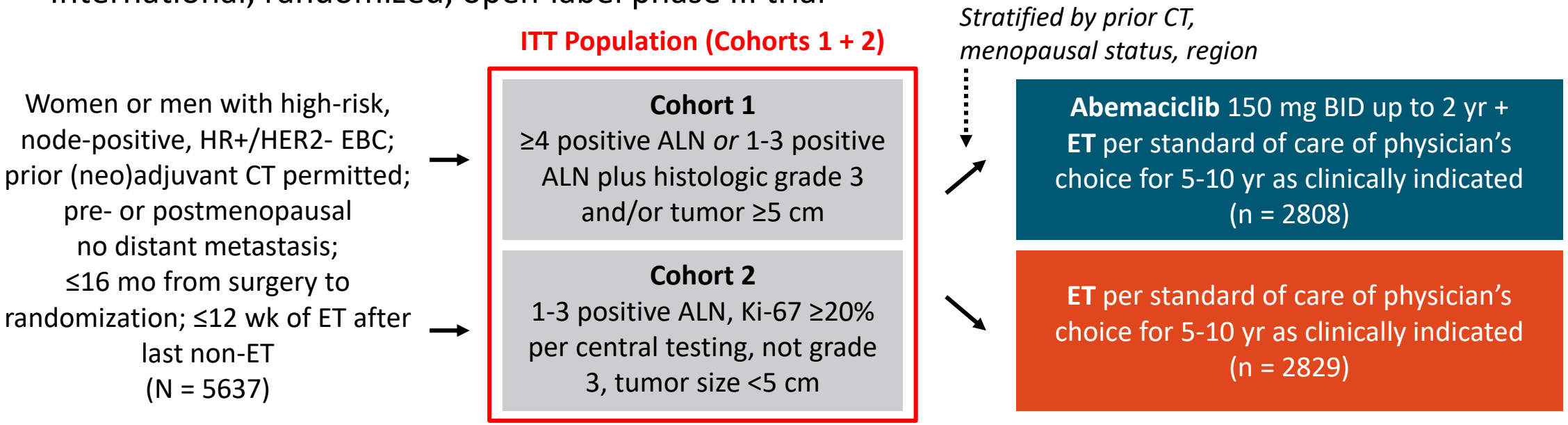
Palbociclib Dose Reductions

- 55% required palbociclib dose reduction to 100 mg, and 34% to 75 mg, at some point during treatment
- Among those discontinuing due to AEs, dose level at time of discontinuation was 75 mg for 62%, suggesting some discontinuations occurred without maximum dose reduction
- Median **exposure intensity** (= intake days / [**26 cycles * 21 intake days**]) of palbociclib was 69.6% (Q1 = 34.6%, Q3 = 95.4%)

Mayer. Lancet Oncol. 2021; 22:212. Mayer. SABCS 2020. Abstr PD2-03

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 hazard ratio of 0.73, cumulative 2-sided $\alpha = 0.05$)
  - 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.

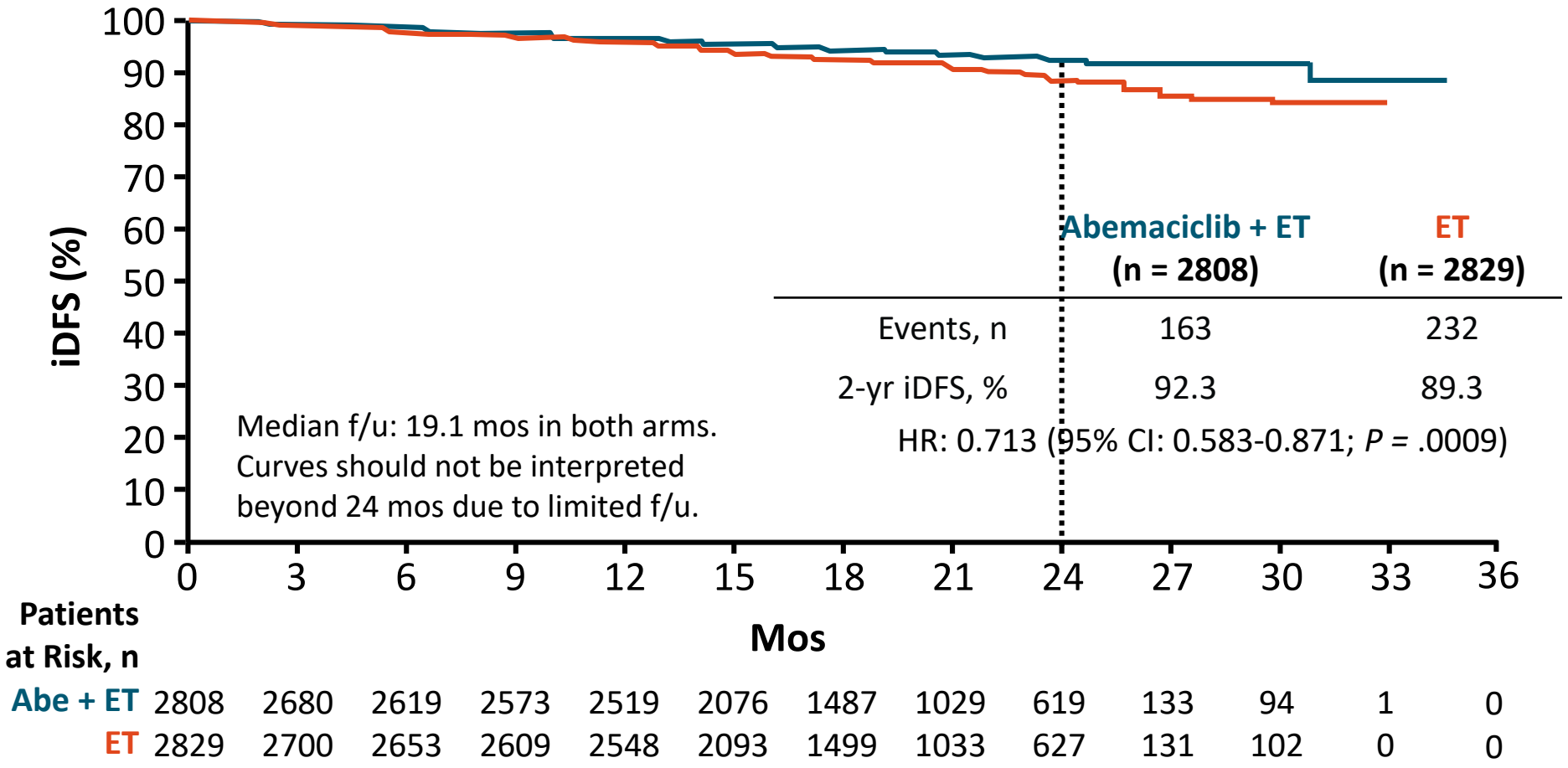
Slide credit: clinicaloptions.com

monarchE: Baseline Characteristics

Characteristic	Abemaciclib + ET (n = 2808)	ET Alone (n = 2829)
Median age, yr (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

monarchE: iDFS (Primary Endpoint)



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

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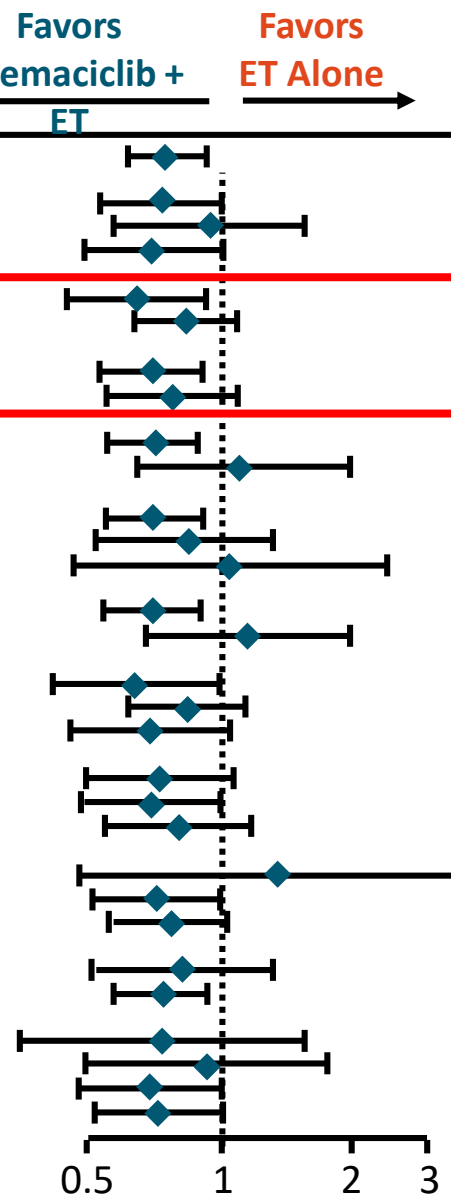
monarchE: iDFS by Subgroup

Subgroup		Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	Hazard Ratio (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, yr	<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	1	209	8	215	6	1.35 (0.47-3.89)
	2	1373	55	1395	81	0.71 (0.50-0.99)
	3	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.

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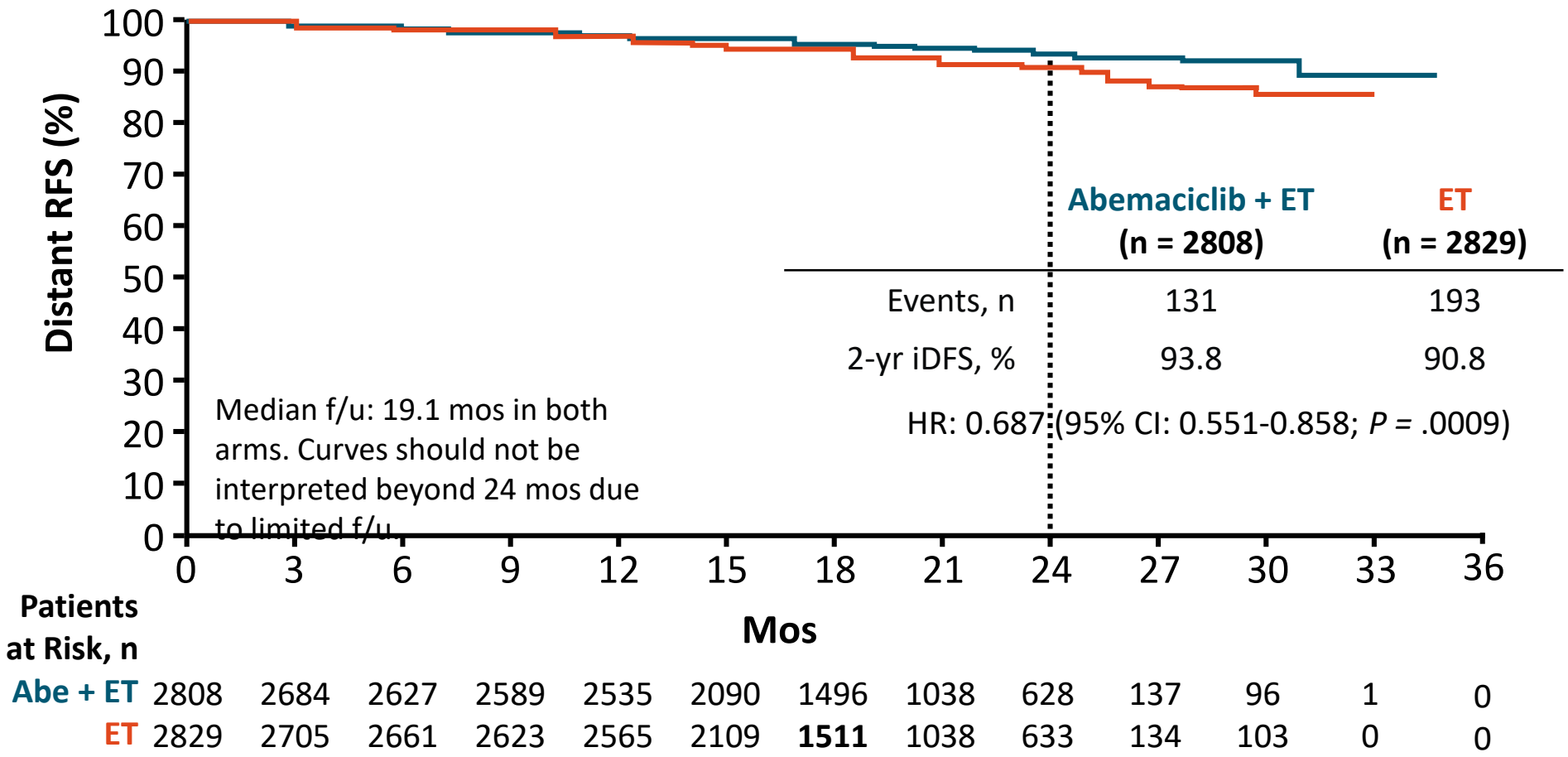
monarchE: Distant RFS



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

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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.

Slide credit: clinicaloptions.com

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.

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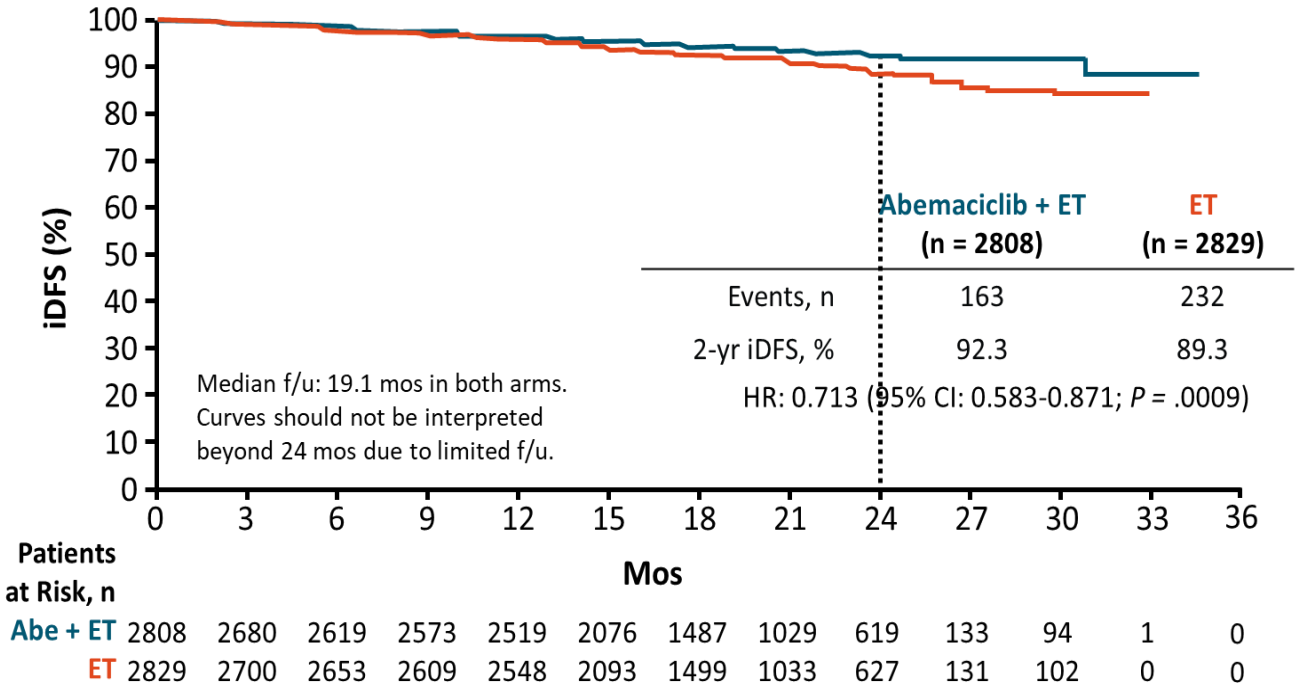
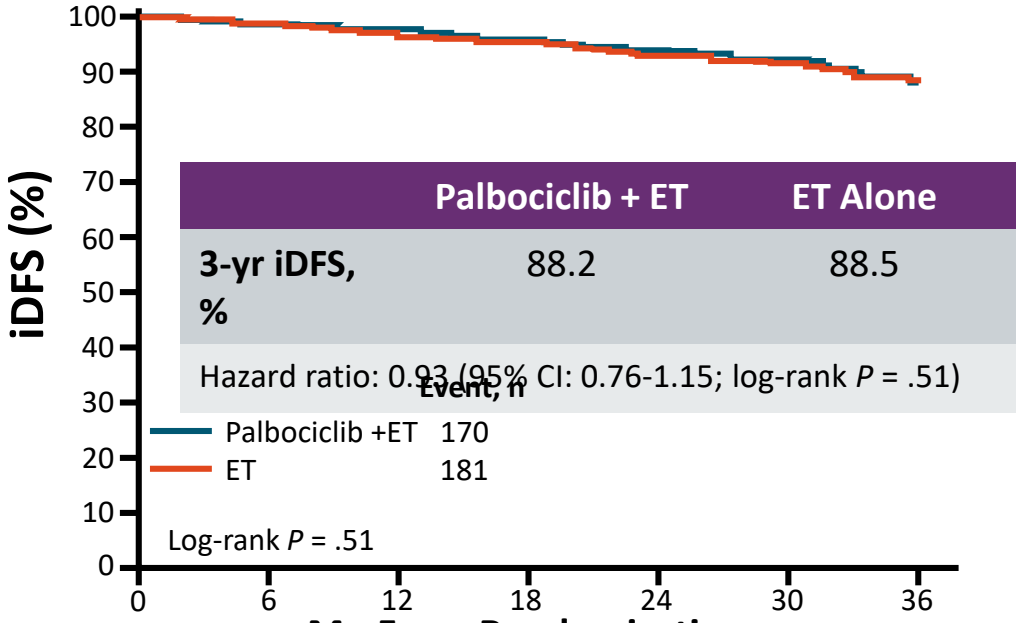
Why Did MonarchE Succeed Where PALLAS Failed?

MonarchE iDFS



Patients at Risk, n													
Abe + ET	2808	2680	2619	2573	2519	2076	1487	1029	619	133	94	1	0
ET	2829	2700	2653	2609	2548	2093	1499	1033	627	131	102	0	0

PALLAS iDFS



Patients at Risk, n							
Palbociclib + ET	2883	2634	2563	1946	1257	583	163
ET alone	2877	2649	2535	1953	1295	574	172

Differences between the drugs themselves/drug exposure and discontinuations/ level of risk within patient populations?

Johnston. JCO. 2020;38:3987. Mayer. ESMO 2020. Abstr LBA12.

Slide credit: clinicaloptions.com

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

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

Stratified by age (≤50 vs >50 yr), nodal status (ypN0-1 vs ypN2-3), Ki-67 (>15% vs ≤15%), region (Asia vs non-Asia), and CPS-EG score (≤3 vs 2 and ypN+)

Adult patients with confirmed HR+/HER2- BC with residual disease after ≥16 wk of neoadjuvant CT*; CPS-EG score ≥3 or 2 with ypN+ (N = 1250)

→ **Surgery ± radiotherapy†**

→ **Palbociclib** 125 mg QD Days 1-21
28-day cycles x 13
+ **ET** by local standard
(n = 631)

→ **Placebo** QD Days 1-21
28-day cycles x 13 +
+ **ET** by local standard
(n = 619)

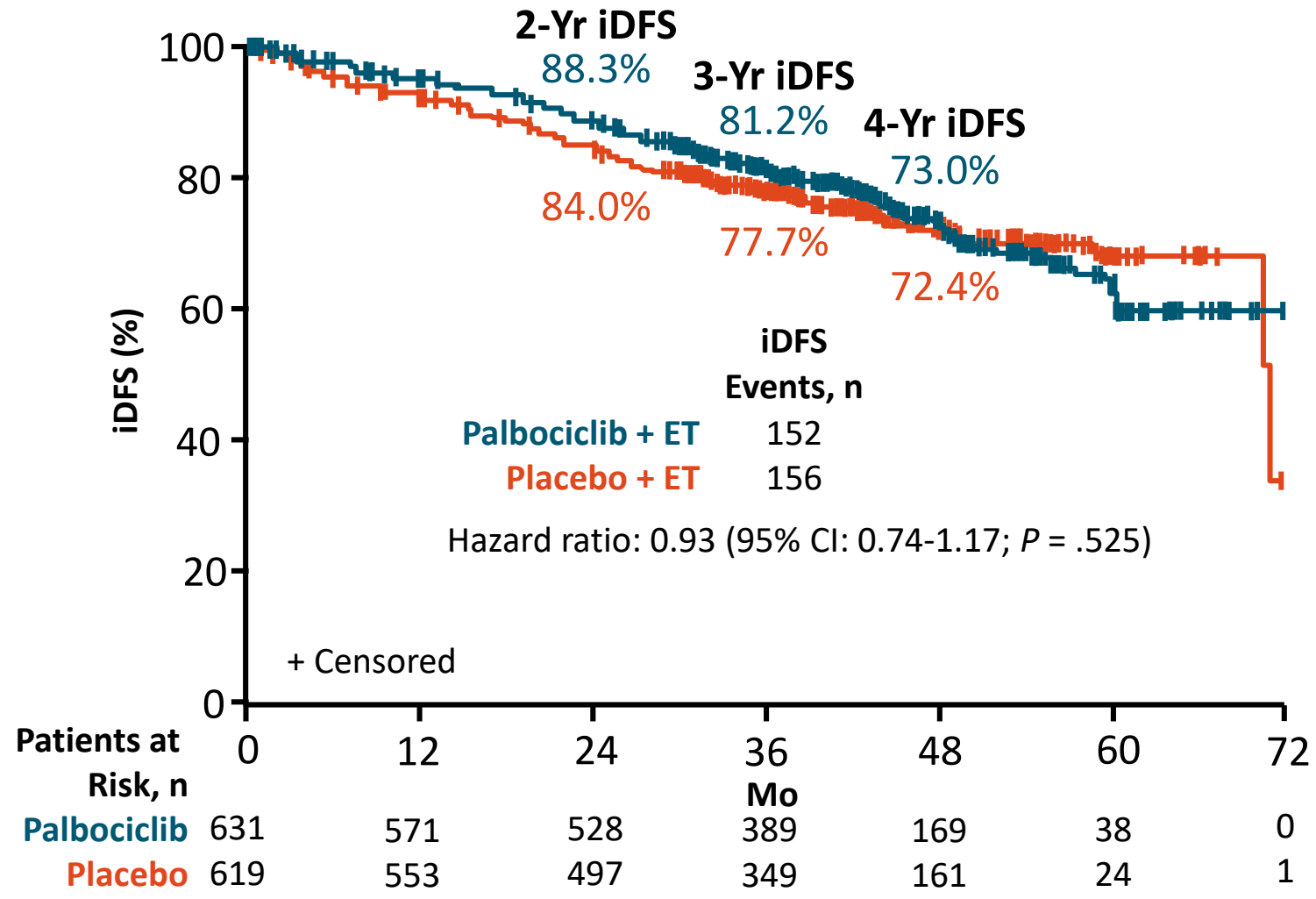
*Includes 6 wk of taxanes.
†Time between locoregional therapy and randomization: <16 wk from final surgery or <10 wk from RT completion.

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

Loibl. JCO 2021;10:1200.

Slide credit: clinicaloptions.com

PENELOPE-B: iDFS (Primary Endpoint)



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

Loibl. JCO 2021;10:1200.

Slide credit: clinicaloptions.com

PENELOPE-B: Patient Disposition and Exposure

Patient Disposition	Palbociclib (n = 631)	Placebo (n = 619)
Started treatment, n	628	616
Completed ≥7 cycles of tx, n (%)	559 (88.6)	559 (90.3)
Completed all 13 tx cycles regularly, n (%)	508 (80.5)	523 (84.5)
Discontinued ET prematurely, n (%)	28 (4.4)	36 (5.8)
Discontinued study tx, %	123 (19.5)	96 (15.5)
▪ Disease recurrence	25 (4.0)	40 (6.5)
▪ Second primary nonbreast cancer	2 (0.3)	3 (0.5)
▪ Death	2 (0.3)	1 (0.2)
▪ Adverse event	33 (5.2)	5 (0.8)
▪ Patient choice	56 (8.9)	41 (6.6)
▪ Investigator choice	5 (0.8)	6 (1.0)

Exposure Parameter	Palbociclib (n = 633)	Placebo (n = 611)	*P* Value
Duration of exposure, wk			
▪ Mean	48.6	48.1	<.001
▪ Median	52.9	52.0	
▪ Range	1.1-70.1	1.4-66.0	
Relative total dose intensity, %			
▪ Mean	75.8	93.0	<.001
▪ Median	82.1	98.9	
▪ Range	0.4-105.9	0.7-104.3	

Loibl. JCO 2021;10:1200.

Slide credit: clinicaloptions.com

CDK4/6 Inhibition in High-Risk HR+/HER2- EBC: Summary

- **monarchE:** In a preplanned interim analysis, **adj abemaciclib + ET continued** to demonstrate improved iDFS vs ET alone for HR+/HER2- EBC at high risk of relapse after locoregional tx and/or (neo)adj CT (hazard ratio: 0.75; 95% CI: 0.60-0.93; *P* = .01)[1,2]
  - 2-yr iDFS rates: 92.2% with abemaciclib + ET vs 88.7% with ET
  - Significant iDFS improvement observed **in Ki-67 high (≥20%)** tumors
  - Distant RFS also improved (hazard ratio: 0.72; 95% CI: 0.56-0.92; *P* = .01), with 2-yr distant RFS rates of 93.6% vs 90.3%, respectively
- **PENELOPE-B:** In the first interim analysis, the addition of 1 yr of adjuvant palbociclib to ET in the curative setting failed to demonstrate a benefit in patients with higher-risk HR+/HER2- EBC after locoregional tx and neoadjuvant CT[3]

1. Johnston. JCO. 2020;38:3987. 2. Rastogi. SABCS 2020. Abstr GS1-01. 3. Loibl. SABCS 2020. Abstr GS1-02.

3 Reported CDKi Adjuvant Trials

	monarchE	PALLAS	PENELOPE-B
N	5637	5600	1250
CDKi	Abemaciclib	Palbociclib	Palbociclib
Eligibility	≥N2 or ≥N1 and G3 or T3 (1) N1 and Ki-67 ≥20% (2)	Anatomic stage 2 or 3 (59% N2 or N1 and G3 or T3)	CPS-EG 3 or 2 with ypN+
CDKi duration, mo	24	24	12
Follow-up, mo	19	24	43
2-yr iDFS (change), %	92 vs 89 (3)	NR	88 vs 84 (4)
3-yr iDFS (change), %	NR	88 vs 89 (-1)	81 vs 78 (3)
4-yr iDFS (change), %	NR	NR	73 vs 72 (.6)
DRFS (change), %	94 vs 91 (3)	89 vs 90 (at Yr 3)	No difference
Discontinuation rate, %	28	42	20
Discontinuation due to AE, %	17	27	5
Completed therapy, %	72	32	80

* 64% of discontinuations.

Rastogi. SABCS 2020. Abstr GS1-01. O'Regan. SABCS 2020. GS1-03. Mayer. ESMO 2020. Abstr LBA12.

Slide credit: clinicaloptions.com

Why Different Outcomes Across These Trials (or Are There)?

- Did definition of "high risk" vary among trials?
  - Was there more **luminal B** (high proliferation) in monarchE than in PALLAS or PENELOPE-B?
- Differences in therapy adherence?
  - May explain PALLAS results but adherence much higher in PENELOPE-B
- Is **abemaciclib** a more effective CDK inhibitor?
  - Possible, although not supported by metastatic first-line trials that have remarkably similar hazard ratios
- Durations of CDKi therapy?
  - **Possible PENELOPE-B** would have been positive if palbociclib had been given for longer
  - Await NATALEE results with 3 yr of ribociclib

O'Regan. SABCS 2020. Abstr GS1-03.

Slide credit: clinicaloptions.com

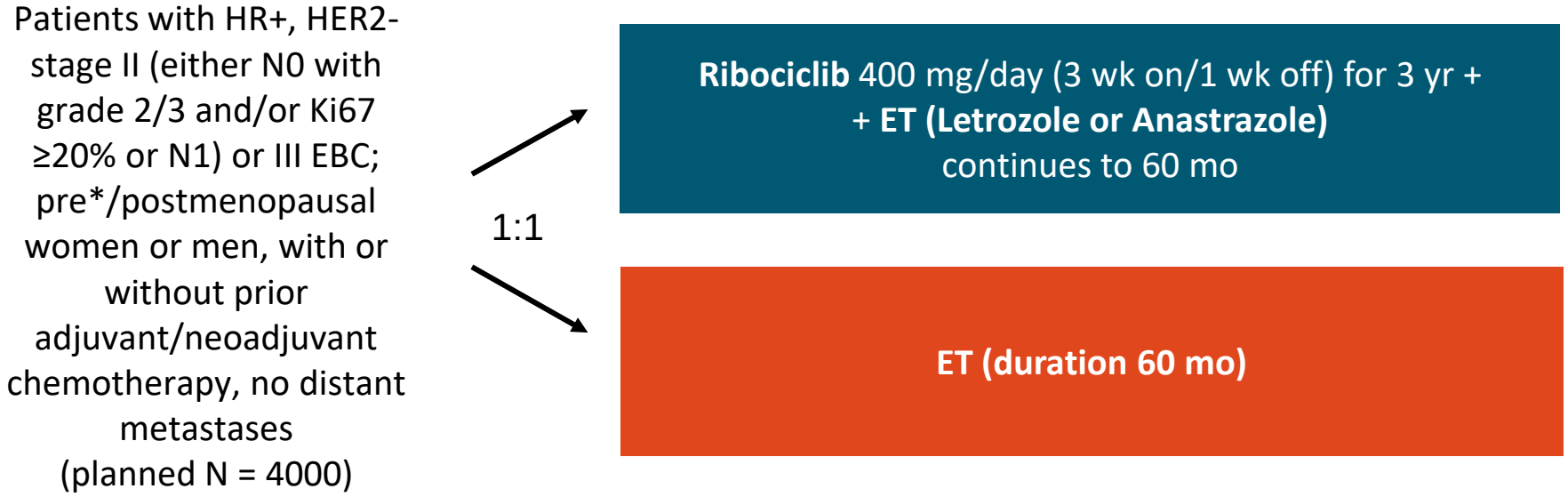
Select Ongoing Trials With CDK4/6 Inhibitors in HR+/HER2- EBC

- Adjuvant ribociclib + ET, phase III, n = 4000
  - NATALEE
- Neoadjuvant abemaciclib + ET vs AC-T chemotherapy, phase II, n = 200
  - CARABELA
- Adjuvant abemaciclib using preoperative AI selection for endocrine resistance, phase III, n = 2500
  - POETIC-A
- Delayed extended adjuvant abemaciclib using clinical/genomic risk selection, phase III, n = 1250
  - ADAPT-LATE

NCT03701334. NCT04293393. NCT04584853. NCT04565054.

Slide credit: clinicaloptions.com

NATALEE: Adjuvant Ribociclib + ET in HR+/HER2- EBC



*Premenopausal and male patients will also receive goserelin 3.6 mg/28 days.

- **Primary endpoint:** invasive disease-free survival (STEEP criteria)
- **Key secondary endpoints:** recurrence-free survival, distant DFS, overall survival, patient-reported outcomes, and RIBO pharmacokinetics; safety and tolerability will also be evaluated

Slamon. ASCO 2019. Abstr TPS597.

Slide credit: clinicaloptions.com

Randomized Phase 3 Clinical Trials Evaluating CDK 4/6 Inhibitors in Early-Stage ER-Positive/HER2-Negative Breast Cancer

Trial Name and Identifier	Estimated Enrollment	Study Treatment	Study Population	Primary Endpoint
PALLAS[a] NCT02513394	5600	Standard adjuvant ET (at least 5 years) ± 125 mg **palbociclib (2 years)**	Stage II (stage IIA limited to maximum of 1000 patients) or stage III Can enroll after 6 months of adjuvant ET	iDFS
PENELOPE-B[b] NCT01864746	1250	Standard adjuvant ET ± **palbociclib** in a 28-day cycle for **13 cycles**	Patients with residual disease and high risk of relapse (based on CPS-EG score) after neoadjuvant chemo of at least 16 weeks	iDFS
NataLEE[c] NCT03701334	5000	Standard adjuvant ET (at least 5 years) ± 400 mg **ribociclib (3 years)**	Stage II/III breast cancer Can enroll after 6 months of adjuvant ET	iDFS
monarchE[d] NCT03155997	4580	Standard adjuvant ET ± 150 mg twice daily **abemaciclib (2 years)**	High-risk node-positive, breast cancer (≥ 4 lymph nodes, tumor > 5 cm, grade 3 or central Ki-67 ≥ 20%) Can enroll after 12 weeks of adjuvant ET	iDFS

Completed (neo)adjuvant chemotherapy and radiation as per institutional guidelines and surgery with clear margins

Role of CDK4/6 Inhibitors in EBC: Questions Raised by Recent Data

In clinical practice how should we identify patients with ER+ EBC at high risk for early/late recurrence?

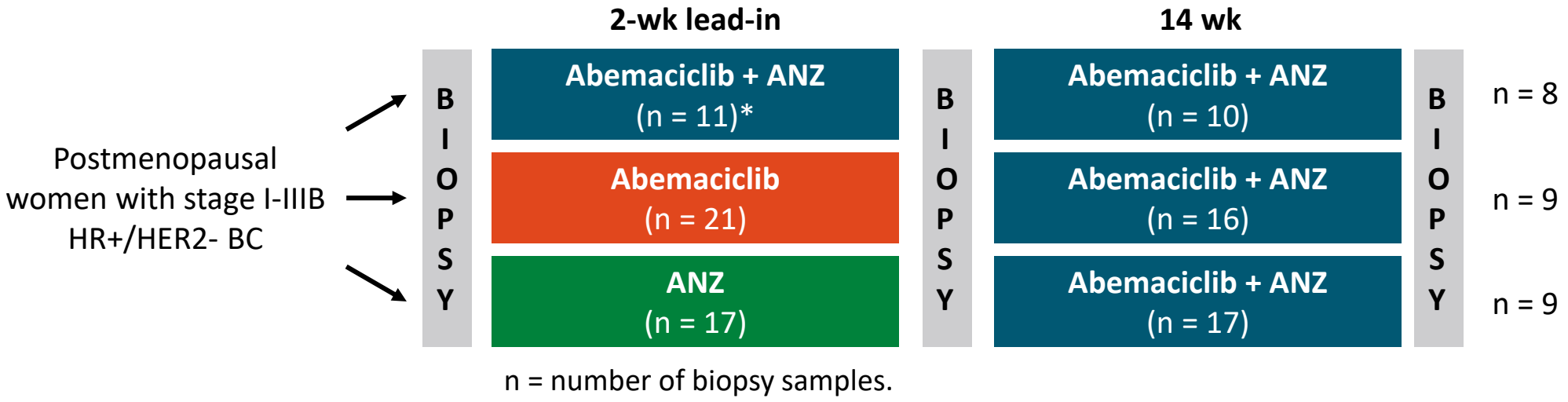
What are the strengths and limitations of recent adjuvant clinical trials?

Can CDK4/6 inhibitors improve clinical outcome in ER+ EBC, and if so, for whom are they indicated?

Slide credit: clinicaloptions.com

neoMONARCH: Neoadjuvant Abemaciclib, Anastrozole, and Abemaciclib + Anastrozole in HR+/HER2- BC

- RNAseq analysis of biopsy samples from multicenter, randomized, open-label phase II trial

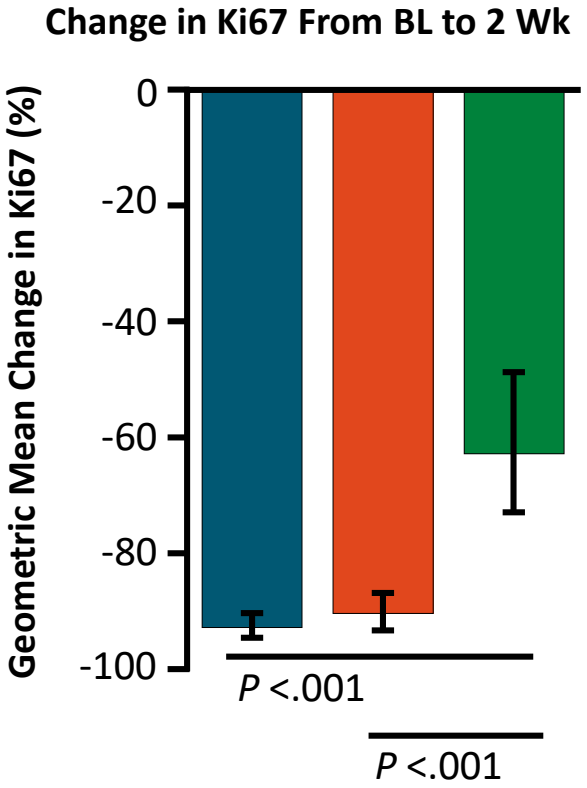


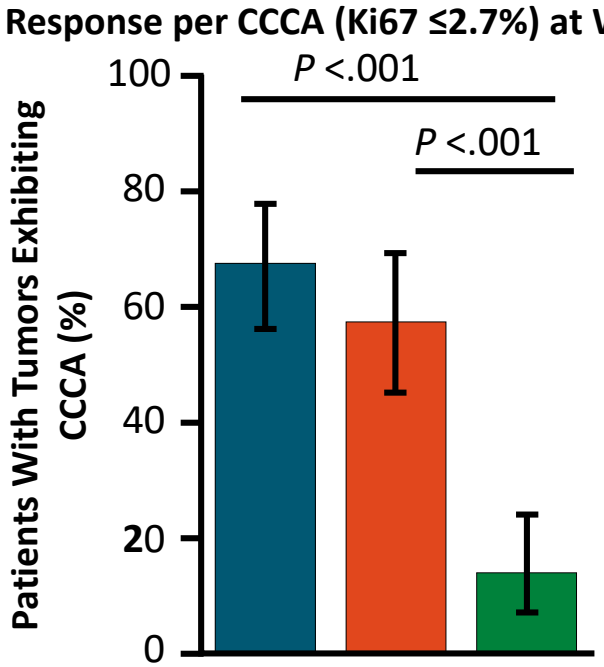
- **Primary endpoint:** percent change in Ki67 from baseline to 2 wk of treatment
- **Secondary endpoints:** pCR, OR, radiologic response

Hurvitz. Clin Cancer Res. 2020;26:566.

Slide credit: clinicaloptions.com

neoMONARCH: Antiproliferative Effects of Abemaciclib, Anastrozole, and Combination Tx on HR+/HER2- BC





Abemaciclib + ANZ (n = 59)
Abemaciclib (n = 52)
ANZ (n = 56)

Abemaciclib + ANZ (n = 40)
Abemaciclib (n = 30)
ANZ (n = 8)

Outcome, %	Abema + ANZ	Abema	ANZ
Geometric mean change in Ki67 at 2 wk	-93	-91	-63
CCCA	68	58	14

- ORR: 46% (5% CR, 42% PR)
- pCR: 4%

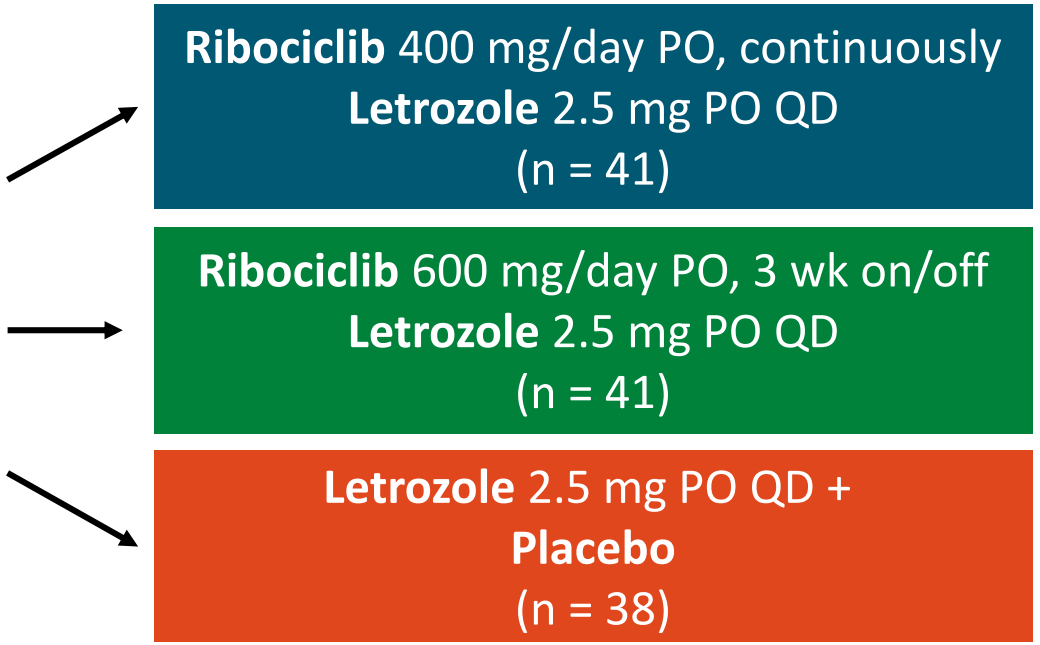
Hurvitz. Clin Cancer Res. 2020;26:566.

Slide credit: clinicaloptions.com

FELINE: Neoadjuvant Ribociclib + Letrozole vs Placebo + Letrozole in ER+/HER2- Breast Cancer

- Randomized, open-label phase II trial (patients accrued Feb 2016 to Aug 2018)

Postmenopausal women with HER2- breast cancer, stage II/III, primary >2 cm; ER+ >66% (N = 120)



- 6 28-day cycles
- Surgery between D8-21 of cycle 6
- Treatment continued until day before surgery
- Clinical response measurement: ultrasound, MRI
- Tissue samples: baseline, Day 14 of cycle 1, and at surgery
- If Ki-67 > 10% at Day 14 of cycle 1, patient removed from trial

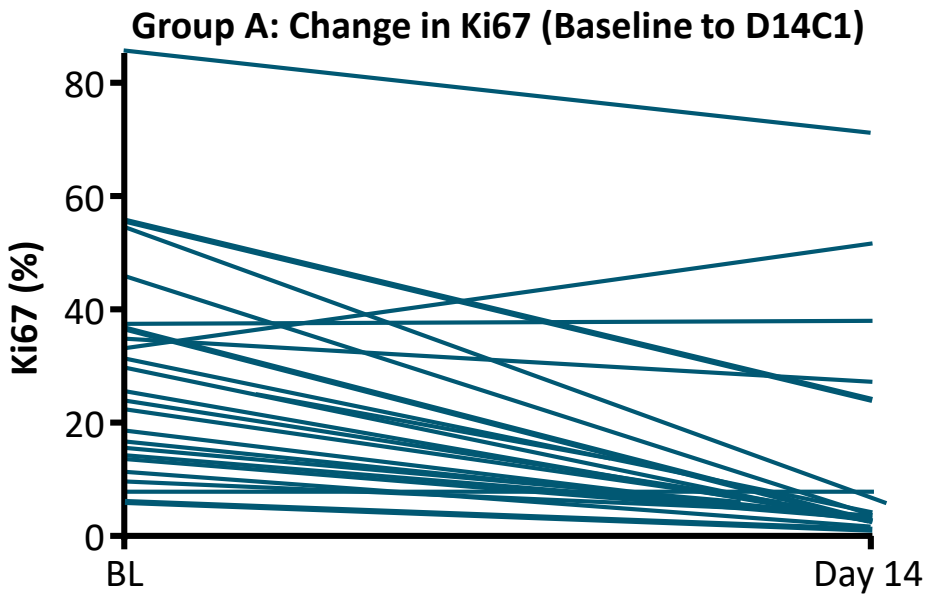
- **Primary endpoint:** Proportion reaching PEPI score 0 at surgery (ie, removing need for adjuvant chemo)
  - PEPI 0: tumor ≤5 cm, node negative, Ki-67 ≤2.7%, Allred ER score 3-8
- **Secondary endpoints:** complete cell-cycle arrest, responses (RECIST), safety

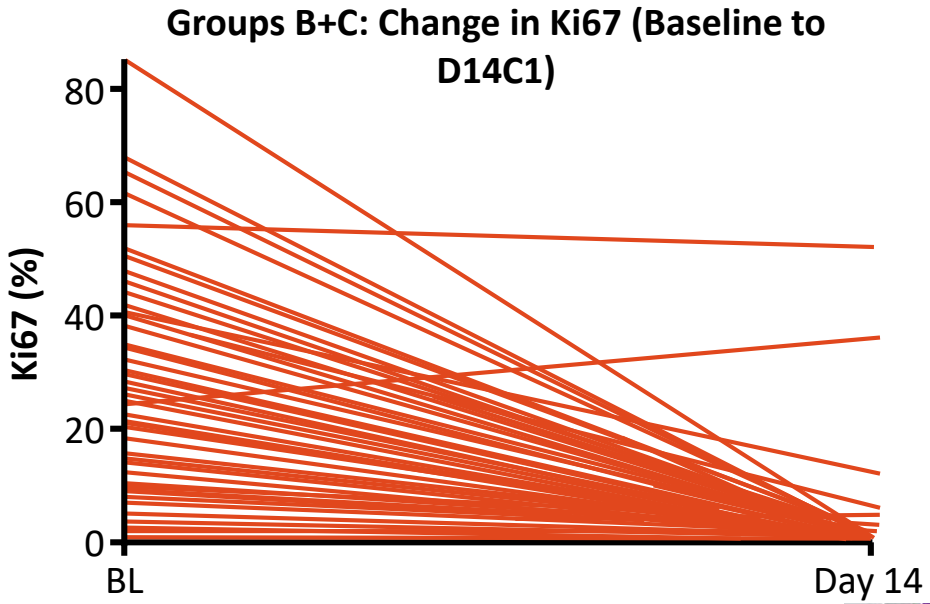
Khan. ASCO 2020. Abstr 505.

Slide credit: clinicaloptions.com

FELINE: Ki67 Change Between Baseline and Day 14 of Cycle 1

Parameter	Group A Placebo + Letrozole	Groups B+C	*P* Value	Group B Ribociclib Intermittent + Letrozole	Group C Ribociclib Continuous + Letrozole
Baseline Ki67, median %	15.8	21.4	.9129	16.5	24.7
Day 14 Ki67 > 10%, % (n/N)	17.24 (5/29)	4.05 (3/74)	.025	2.86 (1/35)	5.13 (2/39)
Mean change Ki67% (baseline to D14C1)	-15.7	-23.3	.047	-20.6	-25.7
CCCA at Day 14, % (n/N)	51.7 (15/29)	91.9 (68/74)	<.0001	97.1 (34/35)	87.2 (34/39)





Khan. ASCO 2020. Abstr 505.

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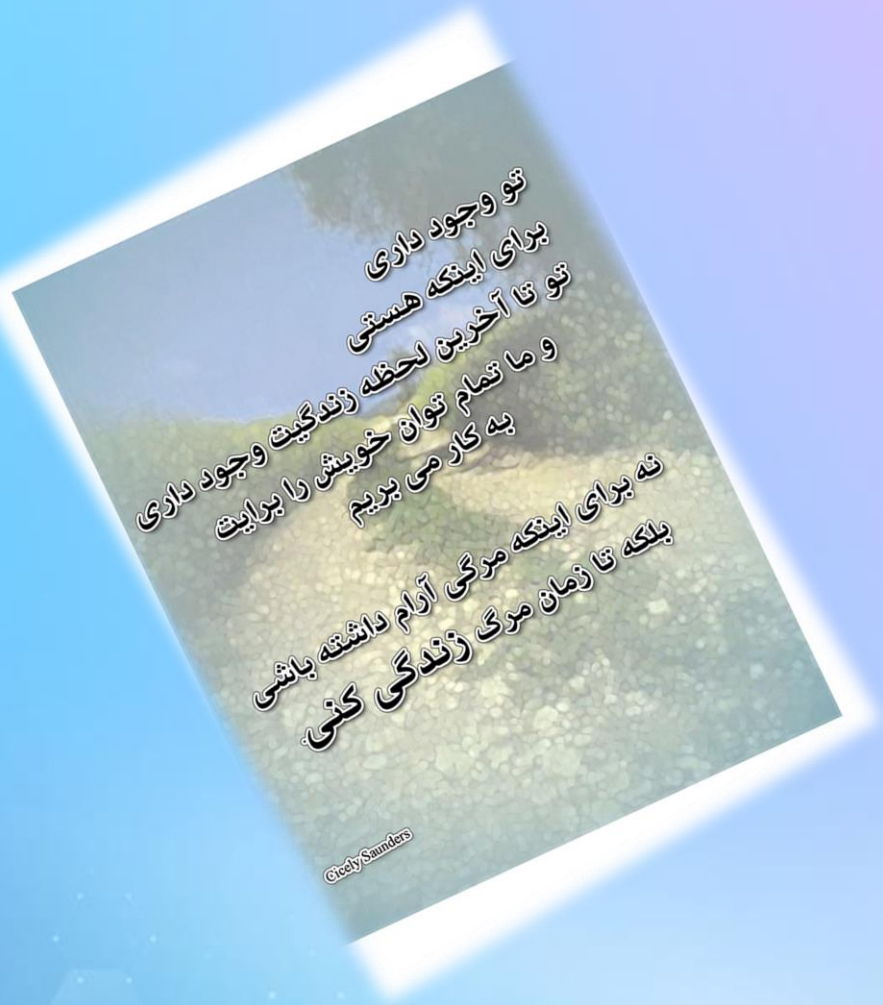

با تشکر

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