Supplementary Appendix

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Table S1. Summary of eligibility criteria and treatment arms of the PALOMA-2 and -3 clinical trials

Study	Patients Cohort	Treatment Arm	
PALOMA-2 (NCT01740427)	**Inclusion** • Postmenopausal women with ER-positive, HER2-negative advanced breast cancer. • No prior systemic therapy for advanced disease. • Adequate organ function, • An ECOG performance status of 0 to 2. • Measurable disease according to RECIST, version 1.1 or lesions only in the bone. **Exclusion** • Patients with advanced, symptomatic, visceral spread who were at risk for short-term, life-threatening complications. • Prior adjuvant or neoadjuvant treatment with a nonsteroidal aromatase inhibitor with disease recurrence or within 12 months of completing therapy. • Known active uncontrolled or symptomatic CNS metastases. • Prior to a CDK inhibitor.	Palbociclib plus letrozole	Oral letrozole 2·5 mg once daily plus oral palbociclib 125 mg, given once daily for 3 weeks followed by 1 week off in 28-day cycles
		Placebo plus letrozole	Oral letrozole 2·5 mg once daily plus oral placebo, given once daily for 3 weeks followed by 1 week off in 28-day cycles
PALOMA-3 (NCT01942135)	**Inclusion** • Women aged 18 years or older of any menopausal status. • An ECOG performance status of 0–1. • Measurable disease according to RECIST, version 1.1 or 1 bone-only disease. • One previous line of chemotherapy in advanced disease was allowed. • Disease relapse or progression had to occur after previous endocrine therapy. **Exclusion** • Patients had extensive symptomatic visceral metastasis and were at risk of life-threatening complications in the short term. • Uncontrolled CNS metastases. • Prior to a CDK inhibitor, fulvestrant, everolimus, or a PI3K/mTOR pathway inhibitor.	Fulvestrant plus palbociclib	Fulvestrant, 500 mg intramuscularly per standard of care every 14 days for the first three injections and then every 28 days and palbociclib, 125 mg per day orally for 3 weeks, followed by 1 week off.
		Fulvestrant plus placebo	Fulvestrant, 500 mg intramuscularly per standard of care every 14 days for the first three injections and then every 28 days and placebo per day orally for 3 weeks, followed by 1 week off.

Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; RECIST, Response Evaluation Criteria in Solid Tumors; CCND1, cyclin D1; ECOG, Eastern Cooperative Oncology Group; CDK, cyclin-dependent kinases; CNS, central nervous system.

Table S2. Censoring reasons for the PALOMA-2 and -3 clinical trials

Study	Outcome	Reason	All	HER2-0			HER2-low-positive		
				All	Palbociclib [a]	Placebo [a]	All	Palbociclib [a]	Placebo [a]
			no. of patients (proportion of censoring %)						
PALOMA-2	Investigator-assessed PFS	***Any reason***	335 (50.3)	86 (56.2)	61 (58.7)	25 (51.0)	249 (48.5)	189 (55.6)	60 (34.7)
		(1) Discontinued treatment without disease progression or death	54	12	9	3	42	28	14
		(2) Given new anti-cancer treatment prior to disease progression and last dose of study treatment	1	0	0	0	1	0	1
		(3) In follow-up for progression	257	66	48	18	191	151	40
		No on-study disease assessments	19	7	3	4	12	9	3
		Unacceptable gap (>30 weeks) between PD or Death to the most recent prior adequate assessment	4	1	1	0	3	1	2
	BICR-PFS	***Any reason***	418 (62.8)	97 (63.4)	65 (62.5)	32 (65.3)	321 (62.6)	227 (66.8)	94 (54.3)
		(1) Discontinued treatment without disease progression or death	149	32	21	11	117	69	48
		(2) Given new anti-cancer treatment prior to disease progression and last dose of study treatment	1	0	0	0	1	0	1
		(3) In follow-up for progression	245	57	40	17	188	148	40
		(4) No on-study disease assessments	2	0	0	0	2	2	0
		(5) No scans/data available	17	8	4	4	9	6	3
		(6) Unacceptable gap (>30 weeks) between PD or Death to the most recent prior adequate assessment	4	0	0	0	4	2	2
PALOMA-3	Investigator-assessed PFS	***Any reason***	325 (62.5)	105 (68.6)	80 (74.8)	25 (54.3)	220 (59.9)	164 (68.6)	56 (43.8)
		(1) Discontinued study without disease progression or death	2	0	0	0	2	2	0
		(2) Given new anti-cancer treatment prior to disease progression and after last dose of study treatment	12	3	2	1	9	6	3
		(3) In follow-up for progression	297	100	76	24	197	151	46
		(4) No adequate baseline assessments	1	0	0	0	1	1	0
		(5) No on-study disease assessments	13	2	2	0	11	4	7
	BICR-PFS	***Any reason***	153 (72.5)	48 (72.7)	33 (80.5)	15 (60.0)	105 (72.4)	88 (83.0)	17 (43.6)
		(1) Given new anti-cancer treatment prior to disease progression and after last dose of study treatment	17	5	4	1	12	9	3
		(2) In follow-up for progression	129	42	29	13	87	74	13
		(3) LF [b]	5	1	0	1	4	4	0
		(4) No on-study disease assessments	2	0	0	0	2	1	1
	OS	***Any reason***	210 (40.4)	59 (38.6)	44 (41.1)	15 (32.6)	151 (41.1)	101 (42.3)	50 (39.1)
		(1) Subject no longer being followed for survival	62	19	13	6	43	22	21
		(2) Subject remains in follow-up	148	40	31	9	108	79	29

Abbreviations: PFS, progression-free survival; OS, overall survival; BICR, blinded independent central review.

[a] The treatment group was Palbociclib or Placebo combined with Letrozole (or Fulvestrant)

[b] LF indicated the censoring reason was redacted in order to reduce the risk of patient re-identification.

Table S3. Median progression-free survival assessed by investigator and median overall survival

Study	HER2 status	Treatment received	no. of PFS events (no. of patients)	mPFS (95% CI)-months [a]	no. of OS events (no. of patients)	mOS (95% CI)-months [a]
PALOMA-2	HER2-0	Palbociclib + Letrozole	43 (104)	NR [16.4, NR]	NA	NA
		Placebo + Letrozole	24 (49)	22.2 [11.0, 24.7]	NA	NA
	HER2-low-positive	Palbociclib + Letrozole	151 (340)	24.8 [22.0, 27.6]	NA	NA
		Placebo + Letrozole	113 (173)	13.8 [11.1, 16.8]	NA	NA
PALOMA-3	HER2-0	Palbociclib + Fulvestrant	27 (107)	NR [7.3, NR]	63 (107)	36.5 [27.2, 43.7]
		Placebo + Fulvestrant	21 (46)	5.4 [3.6, NR]	31 (46)	34.6 [22.2, 39.5]
	HER2-low-positive	Palbociclib + Fulvestrant	75 (239)	8.0 [7.4, 11.0]	138 (239)	34.8 [27.7, 40.4]
		Placebo + Fulvestrant	72 (128)	3.5 [2.1, 5.5]	78 (128)	27.4 [22.2, 33.0]

Abbreviations: NR, not reached; NA, not applicable; CI, confidence interval.

[a] The 95% CI was obtained based on the complementary log-log scale method.

Table S4. Progression-free survival (investigator assessment) rate by landmark time in PALOMA-2 trial

Landmark time (Months)	HER2-0, PFS rate (95% CI)		HER2-low-positive, PFS rate (95% CI)	
	Palbociclib + Letrozole (N=104)	Placebo + Letrozole (N=49)	Palbociclib + Letrozole (N=340)	Placebo + Letrozole (N=173)
3	92% [87%, 97%]	89% [80%, 99%]	92% [89%, 95%]	81% [75%, 87%]
6	86% [79%, 93%]	82% [71%, 94%]	86% [83%, 90%]	70% [63%, 77%]
9	82% [74%, 90%]	72% [60%, 87%]	80% [76%, 84%]	63% [56%, 71%]
12	69% [60%, 79%]	65% [53%, 81%]	74% [69%, 79%]	56% [49%, 64%]
15	62% [53%, 73%]	58% [45%, 75%]	67% [62%, 72%]	48% [41%, 56%]
18	56% [47%, 67%]	54% [40%, 71%]	62% [57%, 68%]	41% [34%, 49%]
21	55% [46%, 66%]	54% [40%, 71%]	57% [52%, 63%]	35% [28%, 44%]
24	53% [43%, 65%]	35% [20%, 62%]	51% [45%, 58%]	27% [20%, 36%]
27	53% [43%, 65%]	28% [14%, 58%]	43% [36%, 52%]	25% [18%, 35%]
30	53% [43%, 65%]	28% [14%, 58%]	41% [33%, 51%]	25% [18%, 35%]
33	NA	28% [14%, 58%]	31% [17%, 56%]	8% [2%, 43%]

Abbreviations: CI, confidence interval; NA, not applicable; PFS, progression-free survival.

Table S5. Progression-free survival (Investigator assessed) and overall survival analyses by treatment groups or by HER2 status

Study	Endpoint	Target	Group	Hazard ratio (95% CI) [a]	P value[a]	Relative excess risk due to interaction [b]
PALOMA-2	PFS	Palbociclib + Letrozole vs. Placebo + Letrozole	All patients	0.57 [0.46, 0.71]	<0.0001	-0.68, (95% CI, -1.43 to 0.08), $p = 0.078$
			HER2-0	0.79 [0.48, 1.30]	0.34	
			HER2-low-positive	0.52 [0.41, 0.66]	<0.0001	
		HER2-low-positive vs. HER2-0	All patients	1.12 [0.86, 1.47]	0.40	
			Palbociclib + Letrozole	0.95 [0.68, 1.34]	0.79	
			Placebo + Letrozole	1.49 [0.96, 2.31]	0.078	
PALOMA-3	PFS	Palbociclib + Fulvestrant vs. Placebo + Letrozole	All patients	0.42 [0.31, 0.55]	<0.0001	0.86, (95% CI, -0.23 to 1.95), $p = 0.12$
			HER2-0	0.54 [0.30, 0.95]	0.034	
			HER2-low-positive	0.39 [0.28, 0.54]	<0.0001	
		HER2-low-positive vs. HER2-0	All patients	1.27 [0.91, 1.76]	0.16	
			Palbociclib + Fulvestrant	1.09 [0.70, 1.70]	0.69	
			Placebo + Fulvestrant	1.56 [0.96, 2.53]	0.075	
	OS	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant	All patients	0.79 [0.63, 1.00]	0.049	-0.04, (95% CI, -0.66 to 0.58), $p = 0.90$
			HER2-0	0.79 [0.51, 1.22]	0.29	
			HER2-low-positive	0.79 [0.60, 1.04]	0.093	
		HER2-low-positive vs. HER2-0	All patients	0.97 [0.76, 1.24]	0.81	
			Palbociclib + Fulvestrant	0.95 [0.71, 1.28]	0.74	
			Placebo + Fulvestrant	1.01 [0.66, 1.53]	0.98	

Abbreviations: CI, confidence interval; PFS, progression-free survival; OS, overall survival.

[a] All the hazard ratios and P value were obtained from unstratified Cox proportional hazards regression models.

[b] Relative excess risk due to interaction (RERI) with 95% CI (by delta method) as a measure of additive interaction, the p-value is obtained based on null hypothesis RERI=0, i.e., no additive interaction.

Table S6. Best overall response in the HER2-0 or HER2-low-positive population using relative risk

Study	Variable	Palbociclib + Letrozole (or Fulvestrant)	Placebo + Letrozole (or Fulvestrant)	Relative risk (95% CI)	*P* value
PALOMA-2	All HER2-0 patients - no.	104	49		
	Rate of objective response - % (95% CI) [a]	36·5 (27·3,46·6)	30·6 (18·3,45·4)	1·19 (0·73,1·95)	0·47
	Rate of clinical benefit response - % (95% CI) [b]	85·6 (77·3,91·7)	73·5 (58·9,85·1)	1·16 (0·97,1·40)	0·071
	All HER2-low-positive patients - no.	340	173		
	Rate of objective response - % (95% CI) [a]	43·8 (38·5,49·3)	35·8 (28·7,43·5)	1·22 (0·97,1·54)	0·082
	Rate of clinical benefit response - % (95% CI) [b]	84·7 (80·4,88·4)	69·4 (61·9,76·1)	1·22 (1·10,1·36)	<0·0001
PALOMA-3	All HER2-0 patients - no.	107	46		
	Rate of objective response - % (95% CI) [a, c]	8·4 (3·9,15·4)	8·7 (2·4,20·8)	0·97 (0·31,2·98)	1·00
	Rate of clinical benefit response - % (95% CI) [b]	24·3 (16·5,33·5)	21·7 (10·9,36·4)	1·12 (0·59,2·12)	0·73
	All HER2-low-positive patients - no.	239	128		
	Rate of objective response - % (95% CI) [a]	11·3 (7·6,16·0)	5·5 (2·2,10·9)	2·07 (0·93,4·61)	0·066
	Rate of clinical benefit response - % (95% CI) [b]	38·5 (32·3,45·0)	18·0 (11·7,25·7)	2·14 (1·43,3·21)	<0·0001

Abbreviations: CI, confidence interval.

[a] Rate of objective response was defined as the percentage of patients who had a confirmed complete response or a partial response. And the exact 95% CI was obtained by the Clopper-Pearson method.

[b] Rate of clinical benefit response was defined as the percentage of patients who had a confirmed complete response, a partial response, or stable disease for 24 weeks or more. And the exact 95% CI was obtained by the Clopper-Pearson method.

[c] There were only four individuals, with HER2-0 and receiving Placebo + Fulvestrant, achieved objective response in PALOMA-3 study, so the corresponding *P* value was obtained by the Fisher's exact test. Other *P* values were obtained by the Pearson χ^2 test.

Table S7. Progression-free survival (investigator assessment) analysis by multivariable Cox proportional hazards model

Study	Model	HER2-0		HER2-low-positive	
		Hazard ratio (95% CI)[a]	P value	Hazard ratio (95% CI)[a]	P value
PALOMA-2	Multivariable model 1[b]	0.69 (0.36, 1.31)	0.25	0.53 (0.42, 0.68)	<0.0001
	Multivariable model 2[c]	0.76 (0.46, 1.26)	0.29	0.53 (0.42, 0.68)	<0.0001
PALOMA-3	Multivariable model 1[b]	0.56 (0.31,1.00)	0.051	0.40 (0.29, 0.55)	<0.0001
	Multivariable model 2[c]	0.59 (0.33, 1.04)	0.070	0.38 (0.28, 0.53)	<0.0001

Abbreviations: CI, confidence interval

[a] The hazard ratio is for Palbociclib+ Letrozole (or Palbociclib + Fulvestrant) versus Placebo + Letrozole (or Placebo + Fulvestrant).

[b] The Multivariable model 1 included the treatment arm and the most imbalance covariate based on Table 1 and Table 2. In PALOMA-2 trial, the most imbalance baseline covariate are 'Most recent therapy' and 'ECOG score at baseline' in HER2-0 and HER2-low-positive population, respectively; In PALOMA-3 trial, the most imbalance baseline covariate are 'Previous lines of therapies for metastatic disease' and 'Histopathological classification' in HER2-0 and HER2-low-positive population, respectively.

[c] The multivariable model 2 included the treatment arm and two covariates, i.e., age (<65 or ≥ 65 years old) and bone-only disease at baseline, per physician's suggestion.

Table S8. Testing proportional hazards assumption for Cox regression

Study	Group	Endpoint	Variable	P value
PALOMA-2	HER2-0	Investigator-assessed PFS	Treatment Group	0.89
		BICR-assessed PFS	Treatment Group	0.69
		Multivariable Model 1	Treatment Group	0.45
			Most recent therapy	0.078
		Multivariable Model 2	Treatment Group	0.96
			Age (<65 or ≥ 65 years old)	0.062
			bone-only disease at baseline	0.42
	HER2-low-positive	Investigator-assessed PFS	Treatment Group	0.34
		BICR-assessed PFS	Treatment Group	0.91
		Multivariable Model 1	Treatment Group	0.41
			ECOG score at baseline	0.75
		Multivariable Model 2	Treatment Group	0.37
			Age (<65 or ≥ 65 years old)	0.46
			bone-only disease at baseline	0.19
PALOMA-3	HER2-0	Investigator-assessed PFS	Treatment Group	0.16
		BICR-assessed PFS	Treatment Group	0.12
		Multivariable Model 1	Treatment Group	0.15
			Previous lines of therapies for metastatic disease	0.97
		Multivariable Model 2	Treatment Group	0.17
			Age (<65 or ≥ 65 years old)	0.45
			bone-only disease at baseline	0.32
		OS	Treatment Group	0.10
	HER2-low-positive	Investigator-assessed PFS	Treatment Group	0.20
		BICR-assessed PFS	Treatment Group	0.80
		Multivariable Model 1	Treatment Group	0.21
			Histopathological classification	0.94
		Multivariable Model 2	Treatment Group	0.28
			Age (<65 or ≥ 65 years old)	0.46
			bone-only disease at baseline	0.95
		OS	Treatment Group	0.63

Abbreviations: CI, confidence interval; PFS, progression-free survival; OS, overall survival; BICR, blinded independent central review.

Table S9. Progression-free survival (investigator assessment) rate by landmark time in PALOMA-3 trial

Landmark time (Months)	HER2-0, PFS rate (95% CI)		HER2-low-positive, PFS rate (95% CI)	
	Palbociclib + Fulvestrant (N=107)	Placebo + Fulvestrant (N=46)	Palbociclib + Fulvestrant (N=239)	Placebo + Fulvestrant (N=128)
2	85% [78%, 92%]	85% [75%, 96%]	84% [79%, 89%]	61% [52%, 70%]
4	73% [63%, 84%]	58% [44%, 77%]	75% [69%, 81%]	43% [35%, 54%]
6	67% [56%, 80%]	42% [27%, 67%]	65% [58%, 73%]	30% [21%, 43%]
8	62% [48%, 79%]	28% [11%, 71%]	49% [38%, 64%]	30% [21%, 43%]
10	62% [48%, 79%]	NA	37% [23%, 60%]	30% [21%, 43%]

Abbreviations: CI, confidence interval; NA, not applicable; PFS, progression-free survival.

Table S10. Overall survival (investigator assessment) rate by landmark time in PALOMA-3 trial

Landmark time (Months)	HER2-0, OS rate (95% CI)		HER2-low-positive, OS rate (95% CI)	
	Palbociclib + Fulvestrant (N=107)	Placebo + Fulvestrant (N=46)	Palbociclib + Fulvestrant (N=239)	Placebo + Fulvestrant (N=128)
6	93% [89%, 98%]	100% [100%, 100%]	95% [92%, 97%]	93% [88%, 97%]
12	85% [78%, 92%]	91% [83%, 100%]	86% [82%, 90%]	83% [76%, 90%]
18	78% [70%, 86%]	84% [74%, 96%]	75% [70%, 81%]	70% [62%, 78%]
24	66% [57%, 76%]	60% [46%, 76%]	65% [59%, 72%]	56% [48%, 66%]
30	55% [46%, 66%]	52% [39%, 70%]	54% [48%, 61%]	45% [37%, 56%]
36	52% [43%, 63%]	44% [31%, 63%]	49% [43%, 56%]	40% [31%, 50%]
42	43% [34%, 54%]	26% [15%, 44%]	42% [36%, 50%]	33% [25%, 43%]
48	30% [21%, 44%]	23% [13%, 41%]	35% [28%, 44%]	30% [23%, 41%]

Abbreviations: CI, confidence interval; NA, not applicable; OS, overall survival.

Figure S1. CONSORT flow diagram

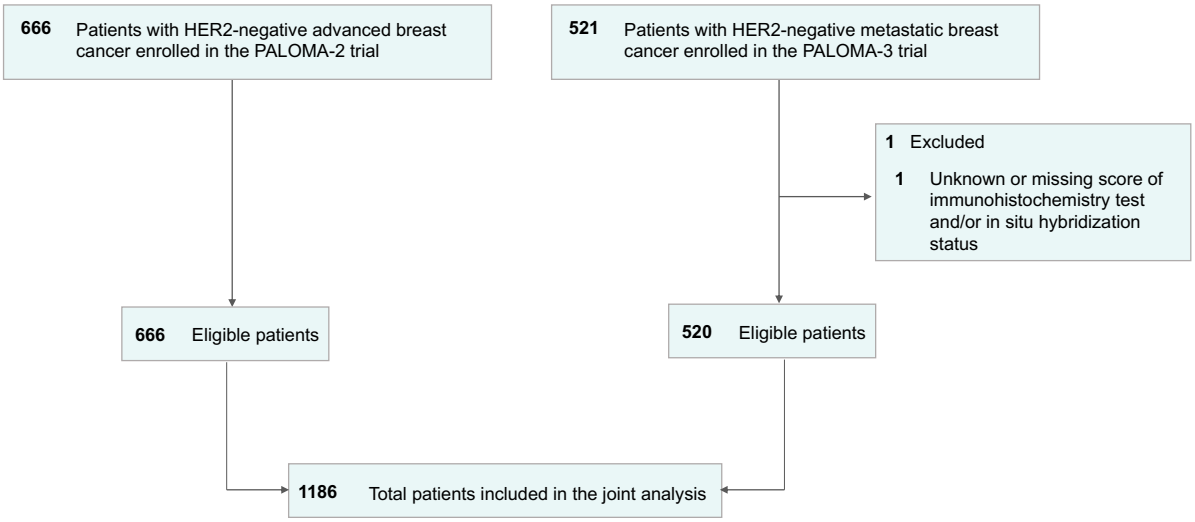
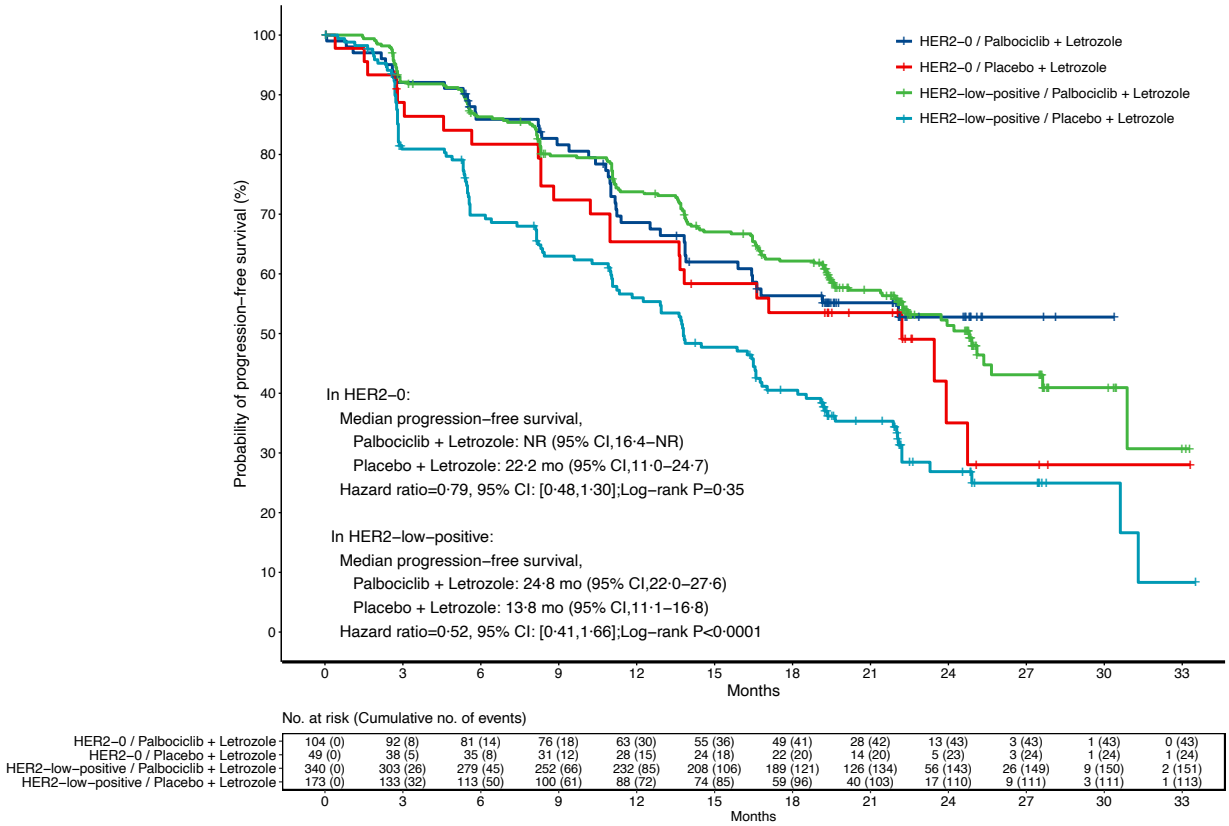


Figure S2. Four Kaplan-Meier curves of progression-free survival assessed by investigator in PALOMA-2 study

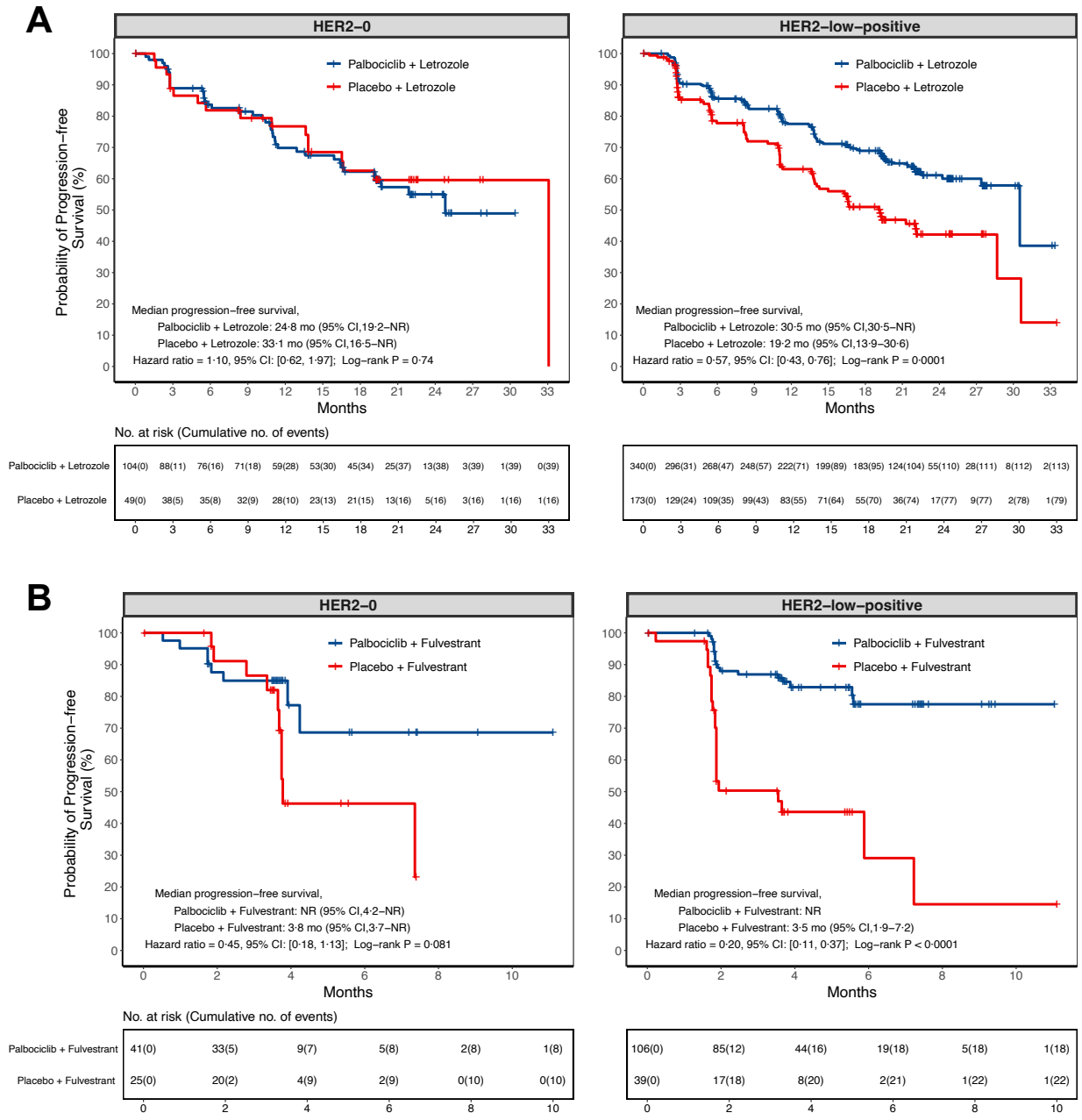


No. at risk (Cumulative no. of events)

HER2–0 / Palbociclib + Letrozole	104 (0)	92 (8)	81 (14)	76 (18)	63 (30)	55 (36)	49 (41)	28 (42)	13 (43)	3 (43)	1 (43)	0 (43)
HER2–0 / Placebo + Letrozole	49 (0)	38 (5)	35 (8)	31 (12)	28 (15)	24 (18)	22 (20)	14 (20)	5 (23)	3 (24)	1 (24)	1 (24)
HER2–low–positive / Palbociclib + Letrozole	340 (0)	303 (26)	279 (45)	252 (66)	232 (85)	208 (106)	189 (121)	126 (134)	56 (143)	26 (149)	9 (150)	2 (151)
HER2–low–positive / Placebo + Letrozole	173 (0)	133 (32)	113 (50)	100 (61)	88 (72)	74 (85)	59 (96)	40 (103)	17 (110)	9 (111)	3 (111)	1 (113)
	0	3	6	9	12	15	18	21	24	27	30	33

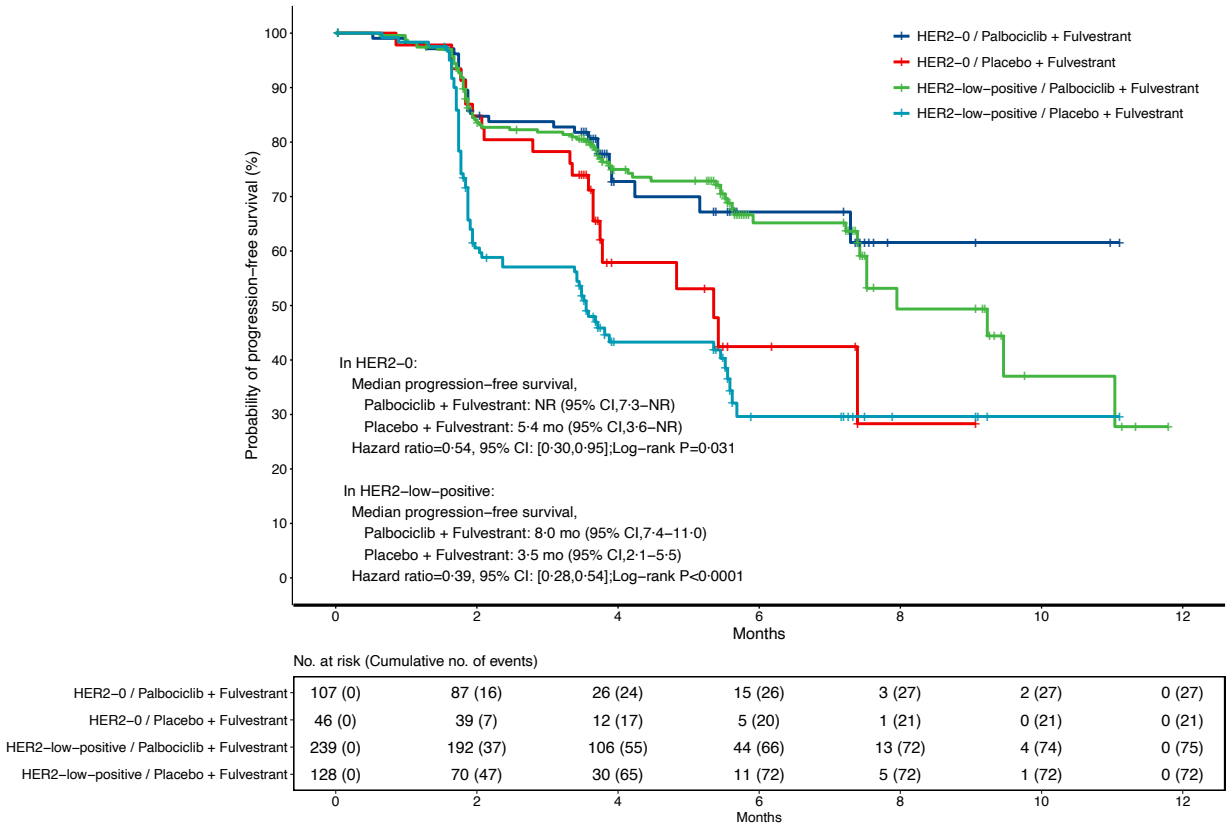
Months

Figure S3. Kaplan-Meier curves of progression-free survival assessed by blinded independent central review



Panel A shows progression-free survival assessed by blinded independent central review in HER2-0 or HER2-low-positive population from PALOMA-2 trial, the relative excess risk due to interaction (RERI)= -0.85 (95% CI: -1.72 to 0.02, p = 0.055 based on null hypothesis RERI=0) with HER2-low-positive and Palbociclib + Letrozole as the reference groups. Panel B shows progression-free survival assessed by blinded independent central review in HER2-0 or HER2-low-positive population from PALOMA-3 trial, the RERI= -2.77 (95% CI: -6.22 to 0.67, p = 0.11 based on null hypothesis RERI=0) with HER2-low-positive and Palbociclib + Fulvestrant as the reference groups.

Figure S4. Four Kaplan-Meier curves of progression-free survival assessed by investigator in PALOMA-3 study



No. at risk (Cumulative no. of events)

	0	2	4	6	8	10	12
HER2–0 / Palbociclib + Fulvestrant	107 (0)	87 (16)	26 (24)	15 (26)	3 (27)	2 (27)	0 (27)
HER2–0 / Placebo + Fulvestrant	46 (0)	39 (7)	12 (17)	5 (20)	1 (21)	0 (21)	0 (21)
HER2–low–positive / Palbociclib + Fulvestrant	239 (0)	192 (37)	106 (55)	44 (66)	13 (72)	4 (74)	0 (75)
HER2–low–positive / Placebo + Fulvestrant	128 (0)	70 (47)	30 (65)	11 (72)	5 (72)	1 (72)	0 (72)

Months