Supplementary Methods

Treatments

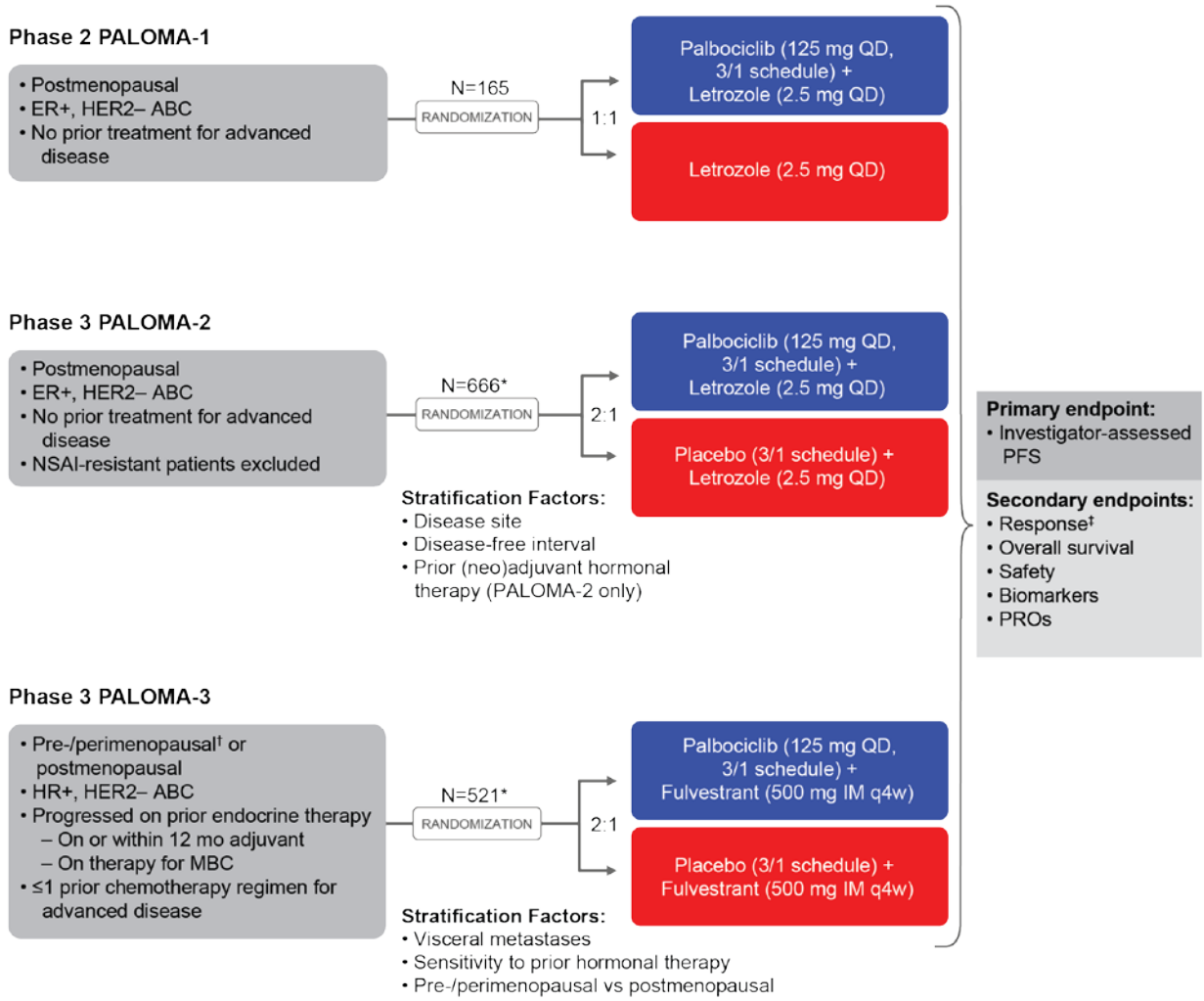
In PALOMA-1, patients were randomly assigned 1:1 to receive either palbociclib (125 mg/d, 3 weeks, 1 week off [3/1 schedule]) plus continuous oral letrozole (2.5 mg/d) or continuous oral letrozole alone. In PALOMA-2, patients were randomly assigned 2:1 to either palbociclib plus letrozole or placebo plus letrozole (same drug doses and schedule tested in PALOMA-1; **Supplementary Figure 1**). In PALOMA-3, patients were randomly assigned 2:1 to receive oral palbociclib (125 mg/d on a 3/1 schedule) plus fulvestrant (500 mg via intramuscular injection on day 1 and 15 of cycle 1 and once every 28-day cycle thereafter) or placebo plus fulvestrant. Pre-/perimenopausal women were required to receive a luteinizing hormone-releasing hormone agonist ≥4 weeks before study entry and goserelin was administered every 28 days throughout the study. For all patients in the PALOMA-1, -2, and -3 studies, the assigned treatment was to be received until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

Adverse Events—Cluster Terms

Anemia includes the preferred terms (PTs) anemia, hematocrit decreased, and hemoglobin decreased; Cutaneous event includes all PTs of the RASH cluster and the PT dry skin; Infections includes any reported PT of the system organ class infections and infestations; Leukopenia includes the PTs leukopenia and white blood cell count decreased; Neutropenia includes the PTs neutropenia and/or neutrophil count decreased; Pulmonary embolism includes the PTs pulmonary artery thrombosis, pulmonary embolism, and pulmonary thrombosis; Rash includes the PTs dermatitis, dermatitis acneiform, rash, rash erythematous, rash maculopapular, rash papular, rash pruritic, and toxic skin eruption; Stomatitis includes the PTs aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth

ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, and stomatitis; Thrombocytopenia includes the PTs platelet count decreased and thrombocytopenia.

Supplementary Figure 1. Study Designs (online only)



Abbreviations: 3/1 schedule, 3 weeks on/1 week off; ABC, advanced breast cancer (includes metastatic breast cancer); ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor (ER+ and/or PR+); IM, intramuscular; MBC, metastatic breast cancer; NSAI, nonsteroidal aromatase inhibitor PFS, progression-free survival; PR, progesterone receptor; PROs, patient-reported outcomes; QD, once daily; q4w, every 4 weeks.

*Actual (not planned) enrollment.

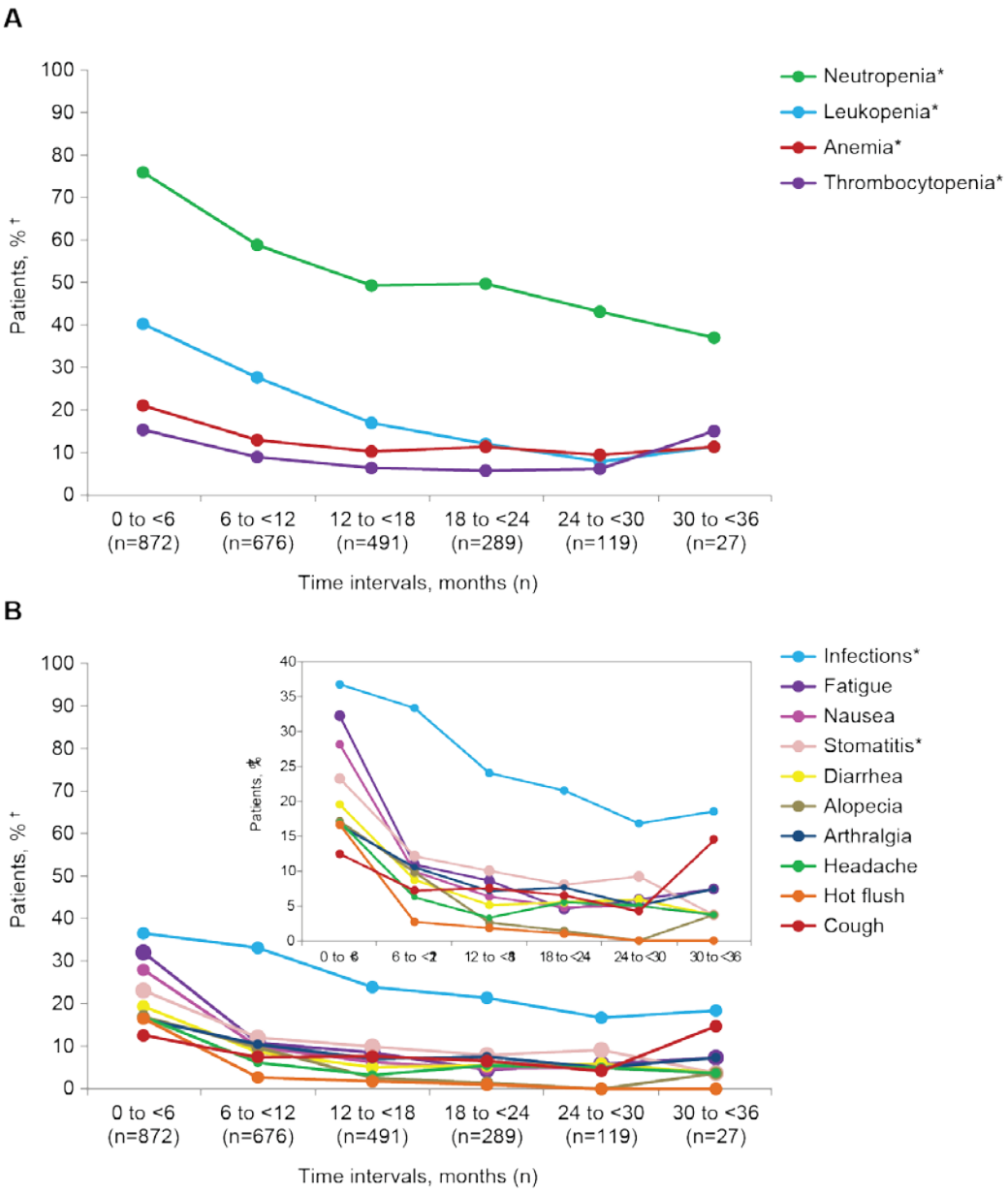
†All received goserelin.

‡Includes overall response (complete response or partial response) and clinical benefit (complete response, partial response, or stable disease for ≥24 weeks) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 (PALOMA-1) or 1.1 (PALOMA-2 and -3). Tumor assessments were performed at screening and every 8 (PALOMA-1 and -3) or 12 (PALOMA-2) weeks; after 1 year, assessments in PALOMA-3 were performed every 12 weeks.

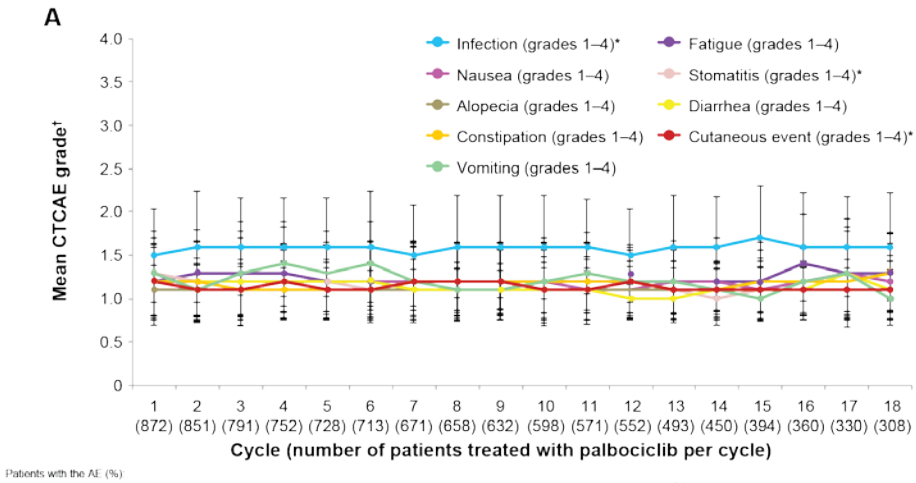
Supplementary Figure 2. Pooled incidence of (A) hematologic and (B) nonhematologic adverse events by 6-month treatment intervals. Includes treatment-emergent adverse events of any grade and all causalities occurring in ≥15.0% of patients treated with palbociclib plus endocrine therapy (online only)

*Cluster terms were used and are defined in the Appendix (online only).

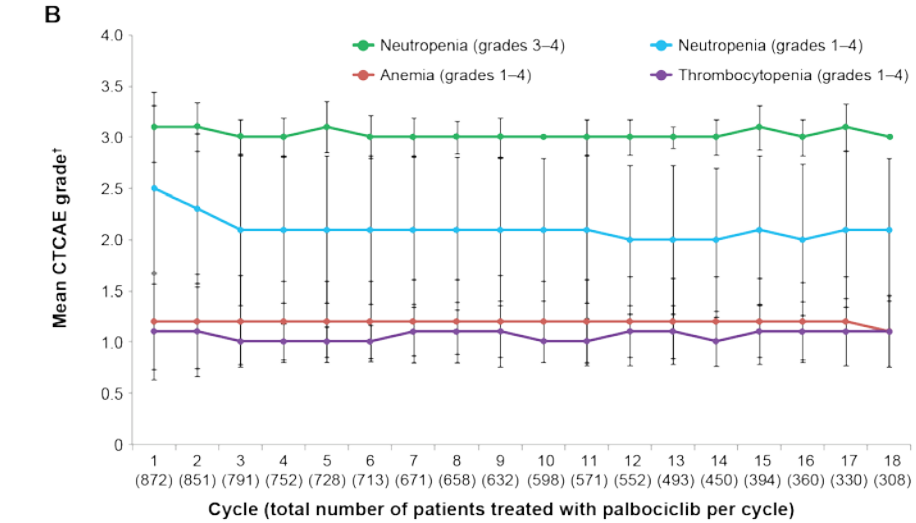
†Patient percentage is calculated using the number of patients at each time interval as the denominator.



Supplementary Figure 3. Mean CTCAE grade by cycle for nonhematologic (A) and hematologic (laboratory-assessed) (B) adverse events (online only)



Patients with the AE (%)																		
Infection	12.5	12.3	11.1	13.2	15.0	15.4	15.8	17.6	15.5	14.7	15.9	17.6	17.2	15.8	15.2	16.9	19.1	17.2
Fatigue	18.3	22.6	23.5	24.6	25.0	25.0	23.8	24.6	26.1	25.9	26.8	27.4	28.6	29.3	28.9	28.9	28.2	26.0
Nausea	18.0	14.9	12.8	10.6	10.0	9.4	9.1	9.6	10.3	10.2	10.2	10.0	9.1	9.3	8.9	10.3	8.8	8.1
Stomatitis*	11.5	11.6	11.6	12.6	12.6	13.5	12.1	12.3	12.0	12.9	12.3	13.0	12.2	12.2	12.2	11.1	12.4	13.8
Alopecia	2.5	6.6	9.0	12.2	15.1	17.0	19.5	21.6	23.4	23.9	24.3	25.7	25.8	28.4	29.4	31.4	32.4	30.8
Diarrhea	11.4	8.6	6.7	6.1	6.5	5.9	6.3	5.3	6.6	7.2	6.7	6.9	6.3	6.7	6.9	6.7	7.6	5.5
Constipation	5.2	8.6	9.1	8.5	8.2	8.0	8.0	8.1	9.2	9.2	10.0	9.4	10.5	11.8	12.4	11.4	11.8	10.4
Vomiting	6.7	4.1	3.5	3.1	3.3	2.8	2.5	2.7	3.2	3.0	1.9	2.5	2.6	2.2	2.3	3.3	2.1	1.0
Cutaneous Event*	8.8	8.7	8.6	7.8	8.9	9.7	10.3	9.7	11.1	12.2	12.1	12.1	12.2	13.1	13.7	14.2	14.2	13.6



Patients with the AE (%)																		
Neutropenia (grade 3–4)	44.7	33.8	22.4	17.6	18.4	18.9	19.4	17.8	17.9	19.1	18.2	18.1	17.0	15.6	20.6	16.4	22.4	18.5
Neutropenia (grade 1–4)	78.6	84.3	68.4	62.5	67.7	66.3	65.7	68.1	65.0	68.6	64.8	67.2	65.1	64.9	64.7	62.2	70.0	65.3
Anemia	48.4	56.8	50.2	49.1	50.4	44.6	43.5	45.9	41.9	42.0	44.1	44.0	40.8	41.8	43.7	39.4	40.3	40.9
Thrombocytopenia	38.3	20.4	23.6	21.1	24.2	25.8	25.2	26.6	24.5	25.3	25.2	26.3	27.0	25.8	28.2	25.8	27.3	25.6

Mean grade (± standard deviation) was calculated based on grade 1–4 events (when applicable) except for neutropenia grades 3–4, which excludes grade 1–2 events. Patients without an event were not included when calculating the means.

*Cluster terms were used and are defined in the Appendix (online only).

†Mean CTCAE grade was calculated based on the adverse event or laboratory result of greatest severity (ie, maximum grade) during a cycle when >1 episode was reported.

AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.

Supplementary Table 1. PALOMA Study Designs—Including Eligibility Criteria (online only)

Study Criteria	PALOMA-1/PALOMA-2	PALOMA-3
Inclusion	• Aged ≥18 years • Postmenopausal • ER+/HER2– advanced breast cancer* • ECOG PS: – 0–1 (PALOMA-1) – 0–2 (PALOMA-2) • No prior systemic treatment for advanced breast cancer – Some (neo)adjuvant treatment per protocol • QTc ≤470 ms (PALOMA-1)	• Aged ≥18 years • Any menopausal status • HR+/HER2– advanced breast cancer • ECOG PS: 0–1 • Endocrine therapy for advanced breast cancer • Progression on endocrine therapy on/within: – 12 mo of adjuvant treatment – 1 mo of endocrine therapy for advanced breast cancer • ≤ 1 prior chemotherapy regimen for advanced breast cancer
Exclusion	• Brain metastasis (PALOMA-1) • Uncontrolled/symptomatic CNS metastasis (PALOMA-2) • Advanced, symptomatic, visceral spread (PALOMA-2) • QTc interval >480 ms (PALOMA-2) • Neo(adjuvant) LET (PALOMA-1) or LET/anastrozole (PALOMA-2) with disease recurrence on/within 12 mo • NSAI resistance (PALOMA-2) • Prior CDK 4/6 inhibitor	• Uncontrolled/symptomatic CNS metastasis • Advanced, visceral spread • QTc interval >480 ms • Prior CDK inhibitor, PI3K-mTOR pathway inhibitor, or fulvestrant

Abbreviations: CDK, cyclin-dependent kinase; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HR, hormone receptor (ER+ and/or PR+); LET, letrozole; mo, month; mTOR, mammalian target of rapamycin; NSAI, nonsteroidal aromatase inhibitor; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; PS, performance status; QTc, QT interval corrected for heart rate.
*Advanced breast cancer includes metastatic disease.