Efficacy and Safety of Palbociclib Plus Fulvestrant in Asian Women With Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That Progressed on Prior Endocrine Therapy

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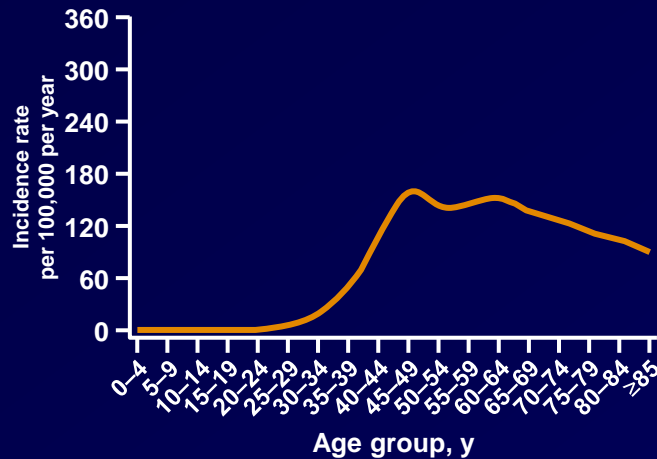
Abstract 1132

Pfizer Oncology

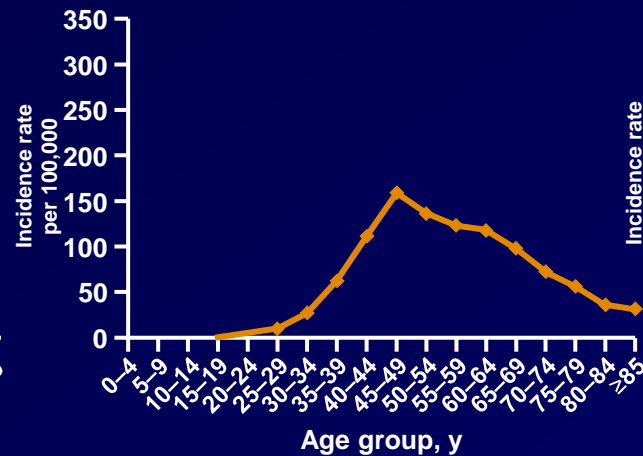# Disclosure Information

- **Conflicts of Interest**
  - Dr Ro has no conflicts of interest to disclose

- **Funding**
  - This study was funded by Pfizer Inc

Age Specific Incidence Rates of Breast Cancer in Women From Asian Countries Versus the US
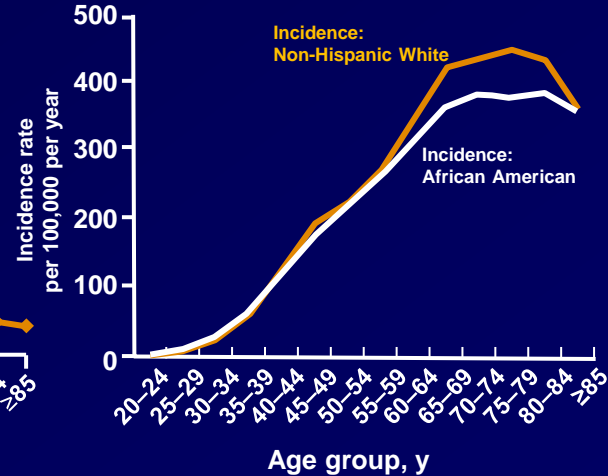
Japan (2004–2008)[1]

Korea (2012)[2]

US (2006–2010)[3]

- **The median age of Asian patients with breast cancer is younger than patients from Western countries including the US[3,4]**

1. Youlden DL, et al. *Cancer Biol Med*. 2014;11:101-115. 2. Jung K-W, et al. *Cancer Res Treat*. 2015;127-141. 3. American Cancer Society. *Breast Cancer Facts & Figures 2013-2014*. Atlanta: American Cancer Society, Inc. 2013. 4. Mousavi-Jarrahi SH, et al. *ISRN Oncol*. 2013;2013:429862

Introduction

- **Endocrine resistance is a major clinical challenge for patients with HR+/HER2– breast cancer**

- **The standard of care is to rechallenge with either ET alone or ET in combination with a targeted agent before switching to chemotherapy**

- **The growth of HR+ breast cancer is facilitated by CDK4 and CDK6[1,2]**

- **Palbociclib is an orally bioavailable small molecule that inhibits CDK4 and CDK6[2]**

- **Palbociclib is active in cell line models of ET resistance and is synergistic with fulvestrant[2]**

CDK = cyclin-dependent kinase; ET = endocrine therapy; HR+ = hormone receptor positive; HER2– = human epidermal growth factor receptor 2 negative

1. Anders L, et al. *Cancer Cell.* 2011;20:620-634. 2. Palbociclib. Full prescribing Information, Pfizer Inc. New York, NY, 2015

PALOMA-3 Study Design

2:1 Randomization

N=521‡

n=347

n=174

- HR+, HER2– ABC
- Premenopausal/perimenopausal*† or postmenopausal†
- Progressed on prior ET
  – On or within 12 mo adjuvant
  – On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

Palbociclib (125 mg QD; 3 wk on/1 wk off) + Fulvestrant § (500 mg IM Q4W)

Placebo (3 wk on/1 wk off) + Fulvestrant § (500 mg IM Q4W)

*All received goserelin
†Must have progressed on prior endocrine therapy (premenopausal/perimenopausal) or aromatase inhibitor therapy (postmenopausal)
‡Patients randomized
§ Administered on days 1 and 15 of cycle 1, then every 28 d

ABC = advanced breast cancer; ET = endocrine therapy; HR+ = hormone receptor positive; HER2– = human epidermal growth factor receptor 2 negative; IM = intramuscular; Q4W = every 4 weeks; QD = once daily

Turner NC, et al. *N Engl J Med*. 2015;373:209-219

PALOMA-3 in Asia

- **In April 2015, IDMC recommended stopping the PALOMA-3 trial early based on significant efficacy (median follow-up, 5.6 months)[1]**

  - **Primary results published by Turner NC, et al[1]**

- **Updated analysis (March 2015 data cut-off) showed a median PFS of 9.5 vs 4.6 months (HR, 0.46; *P*<0.0001) for palbociclib + fulvestrant vs placebo + fulvestrant in in the overall population (median follow-up, 8.9 months)[2]**

  - **The current analysis uses this cutoff**

- **This is the first analysis presenting the efficacy and safety of palbociclib in Asian patients from PALOMA-3 and includes the largest data set to date**

- **Of particular relevance**

  - **Younger age in the Asian vs non-Asian cohorts**

  - **In phase 3 trials involving various drugs, a different toxicity profile in Asian patients compared with patients of other ethnicities has been reported**

HR = hazard ratio; IDMC = Independent Data Monitoring Committee; PFS = progression-free survival

1. Turner NC, et al. *N Engl J Med*. 2015;373:209-219. 2. Cristofanilli M, et al. Poster P4-13-01. San Antonio Breast Cancer Conference; December 8–12, 2015; San Antonio, TX

Demographics and Baseline Disease Characteristics

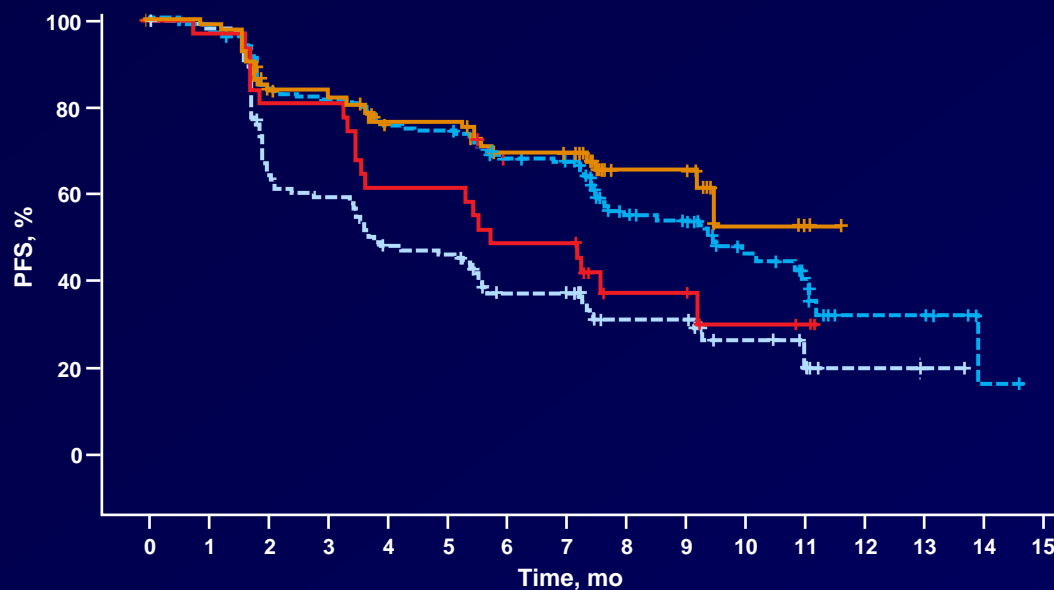| Characteristic	Asian (n=105)	Non-Asian (n=416)
Median (range) age, y	52 (34–82)	58 (29–88)
<55, n (%)	59 (56)	169 (41)
≥55, n (%)	46 (44)	247 (59)
Menopausal status, n (%)		
Premenopausal or perimenopausal	44 (42)	64 (15)
Postmenopausal	61 (58)	352 (85)
Race, n (%)		
Asian	105 (100)	0
White	0	385 (93)
Black or other	0	29 (7)
Median (range) weight, kg	56 (35–83)	72 (43–142)
Median (range) height, cm	155 (140–174)	163 (122–183)
ECOG performance status, n (%)		
0	73 (70)	249 (60)
1	32 (31)	167 (40)
Measurable disease present, n (%)	87 (83)	319 (77)
Documented sensitivity to prior hormonal therapy, n (%)	84 (80)	326 (78)
Prior chemotherapy as metastatic treatment, with or without prior neoadjuvant or adjuvant therapy, n (%)	35 (33)	142 (34)
Previous hormonal regimen for primary diagnosis, n (%)		
1	33 (31)	178 (43)
>1	72 (69)	238 (57)
Prior tamoxifen, n (%)	77 (73)	237 (57)
Prior aromatase inhibitors, n (%)	78 (74)	369 (89)

ECOG = Eastern Cooperative Oncology Group

AEs (≥15% Incidence in Asian Palbociclib-Fulvestrant Group)—All Cause

AE, n (%)	Asian		Non-Asian	
	Palbociclib + Fulvestrant (n=73)	Placebo + Fulvestrant (n=31)	Palbociclib + Fulvestrant (n=272)	Placebo + Fulvestrant (n=141)
Any AE	73 (100)	29 (94)	267 (98)	125 (89)
Hematologic AEs				
Neutropenia*	67 (92)	2 (7)	212 (78)	4 (3)
Leukopenia[†]	33 (45)	1 (3)	138 (51)	6 (4)
Anemia[‡]	18 (25)	3 (10)	78 (29)	16 (11)
Thrombocytopenia[§]	19 (26)	–	54 (20)	–
Nausea	22 (30)	7 (23)	90 (33)	40 (28)
Stomatitis[¶]	19 (26)	2 (7)	24 (9)	2 (1)
Rash[¶]	18 (25)	–	17 (6)	8 (6)
Nasopharyngitis[¶]	15 (21)	3 (10)	26 (10)	9 (6)
Fatigue[¶]	14 (19)	6 (19)	121 (45)	43 (31)
Alopecia	13 (18)	2 (7)	45 (17)	9 (6)
Decreased appetite	13 (18)	2 (7)	39 (14)	12 (9)
Headache	13 (18)	7 (23)	67 (25)	26 (18)
Vomiting	13 (18)	2 (7)	45 (17)	23 (16)
Constipation	13 (18)	3 (10)	53 (20)	24 (17)
Diarrhea	12 (16)	3 (10)	62 (23)	29 (21)
Pyrexia	12 (16)	1 (3)	26 (10)	8 (6)
Cough	11 (15)	2 (7)	40 (15)	20 (14)

*Event cluster consisting of the preferred terms (PTs) of neutropenia and neutrophil count decreased; [†]Event cluster consisting of the PT of leukopenia and white blood cell count decreased; [‡] Event cluster consisting of the PT of anemia, hematocrit decreased, and hemoglobin decreased; [§]Event cluster consisting of the PT of platelet count decreased or thrombocytopenia; [¶]The majority of AEs were grade 1 and 2

AE = adverse event
Date of data cut-off: March 16, 2015

Primary Endpoint: Investigator-Assessed PFS

	Asian	
	Palbociclib + Fulvestrant n=74	**Placebo + Fulvestrant n=31**
HR (95% CI)	0.485 (0.270–0.869)	
1-sided *P* value	0.0065	

	Non-Asian	
	Palbociclib + Fulvestrant n=273	**Placebo + Fulvestrant n=143**
HR (95% CI)	0.451 (0.343–0.593)	
1-sided *P* value	<0.0001	

Patients at Risk, n

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Asian	74	72	62	61	55	55	44	43	20	20	5	4	0			
	31	30	25	25	19	19	15	15	6	6	3	2	0			
Non-Asian	273	261	219	212	192	189	158	154	71	65	27	19	7	7	1	0
	143	135	87	80	64	61	44	43	16	16	10	5	2	1	0	

HR = hazard ratio; PFS = progression-free survival
Date of data cut-off: March 16, 2015

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Secondary Endpoints: Response Assessment
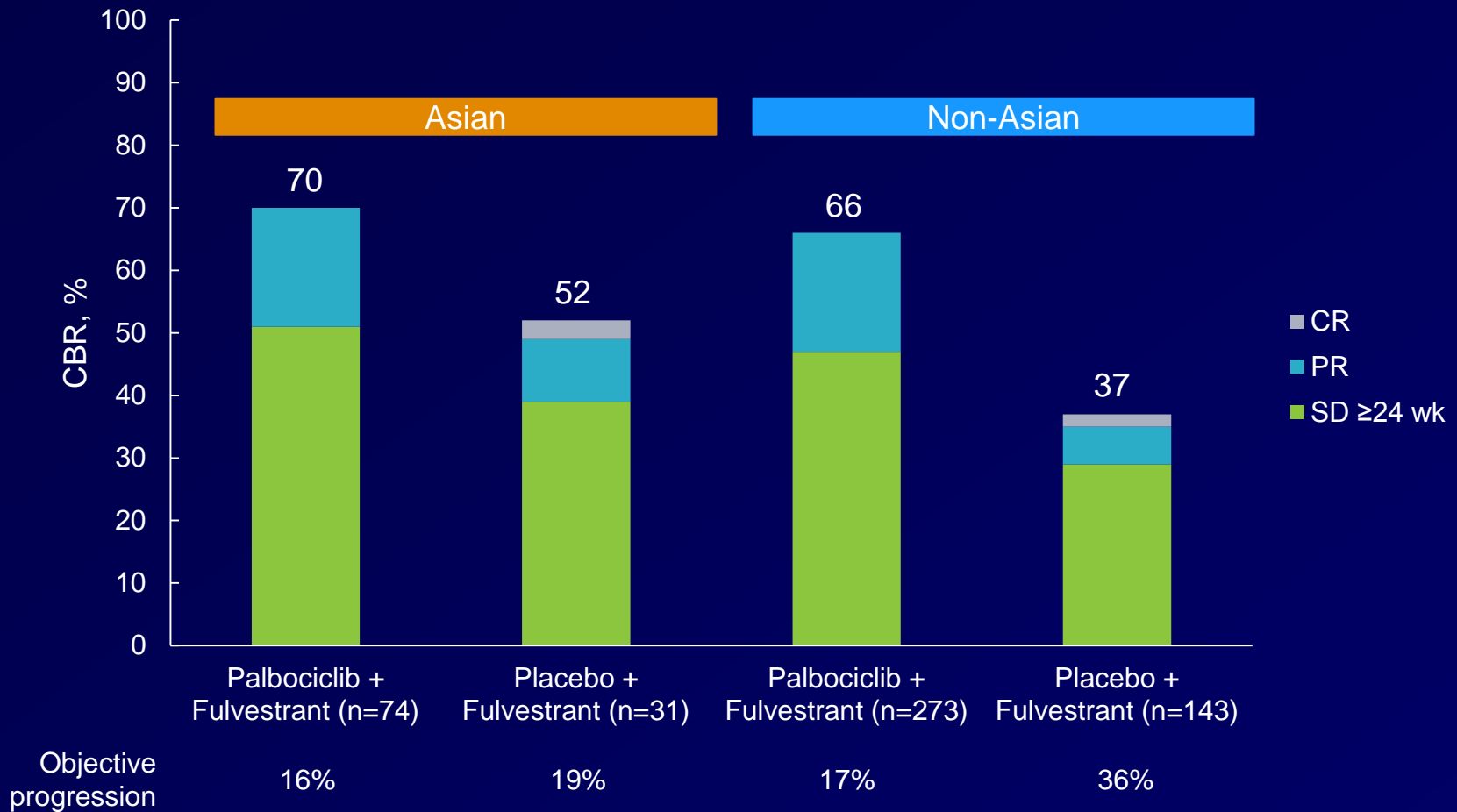
CBR = clinical benefit response rate; CR = complete response; PR = partial response; SD = stable disease
Date of data cut-off: March 16, 2015

Dose Reductions and Dose Delays

	Asian		Non-Asian	
	Palbociclib + Fulvestrant	**Placebo + Fulvestrant**	**Palbociclib + Fulvestrant**	**Placebo + Fulvestrant**
Median (range) relative dose,* %	87 (51–102)	100 (88–100)	98 (25–107)	100 (70–107)
Patients with interruptions due to AE, n (%)	60 (82)	3 (10)	127 (47)	7 (5)
Median (range) number of interruptions per patient	2 (1–23)	1 (1–1)	2 (1–8)	1 (1–2)
Patients with cycle delay due to AE, n (%)	37 (51)	0	86 (32)	3 (2)
Median (range) number of cycle delays per patient	2 (1–4)	1 (1–1)	1 (1–5)	1 (1–1)

*Relative dose = [(actual dose)/(intended dose)] × 100%

AE = adverse event
Date of data cut-off: March 16, 2015

Summary of Adverse Events

- **In Asian patients, the overall incidence of SAEs (any cause) was similar between arms**
  - 14% (10 of 73 patients) for palbociclib + fulvestrant vs 23% (7 of 31 patients) for placebo + fulvestrant
- **Incidence of febrile neutropenia was 4% (3* of 73 patients) in the palbociclib + fulvestrant arm**
- **Palbociclib + fulvestrant treatment in Asian patients resulted in slightly increased rates of neutropenia, stomatitis, rash, and nasopharyngitis compared with non-Asian patients**
- **Most AEs were mild or moderate in severity**
- **No patient discontinued palbociclib + fulvestrant owing to AEs**
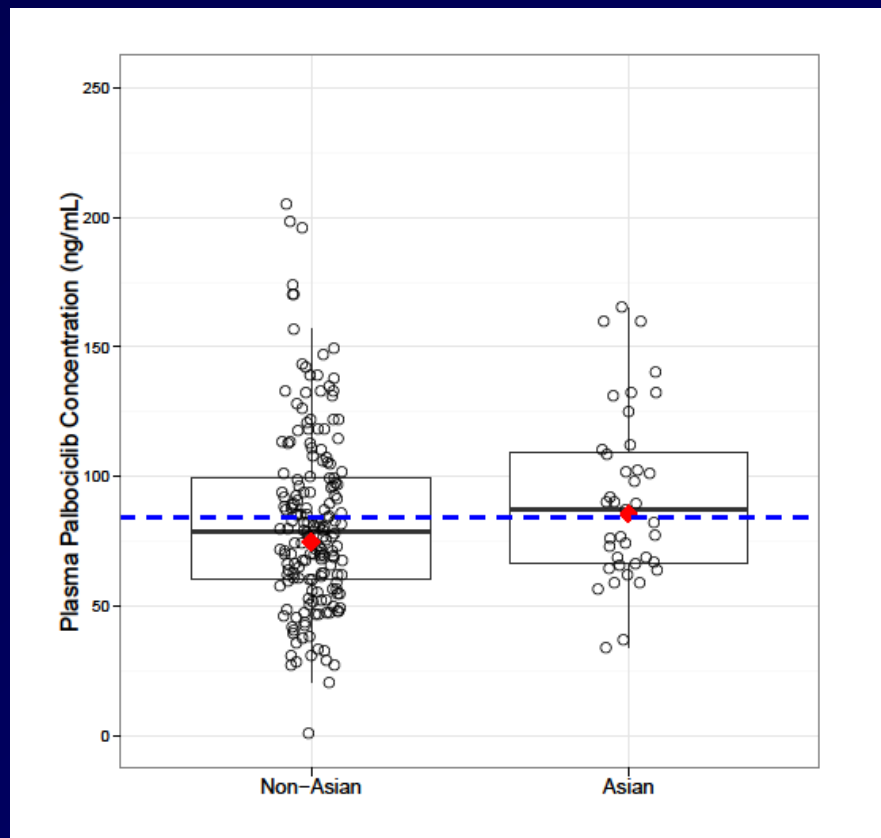- **No deaths due to AEs/toxicity occurred**

*3 cases of febrile neutropenia occurred, of which 2 cases were reported as SAE
AE = adverse event; SAE = serious adverse event

Palbociclib PK Data in Asian vs Non-Asian Patients

- **No differences in C_{max} exposure at steady state were observed between non-Asian and Asian patients by geometric mean values**

- **A population PK-PD analysis performed to assess the exposure-response relationship for neutropenia within the PALOMA-3 study found that Asian race, baseline ALT, and age were significant covariates on the baseline ANC values**

- **Generally, Asian patients had a baseline ANC value 19% lower than a non-Asian patients, which may partially explain the higher rate of neutropenia observed in the Asian population**

Red diamonds represent the sub-population geometric mean values and open circles represent individual patient values. Dashed blue line represents the arithmetic mean value of all data from all patients.
Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times interquartile range

ALT = alanine aminotransferase; ANC = absolute neutrophil count; C_{max} = maximum serum concentration; PD = pharmacodynamic; PK = pharmacokinetic

Conclusions

- **Palbociclib + fulvestrant improved PFS in Asian patients with HR+/HER2– MBC that progressed on prior endocrine therapy**
- **The safety profile of palbociclib + fulvestrant in Asian patients was generally consistent with that seen in non-Asian patients**
  - **Neutropenia was the most commonly reported AE, and the rate was higher in Asian vs non-Asian patients**
    - **Neutropenia could be managed using a dose modification strategy**
    - **The incidence of febrile neutropenia was low**
  - **Most AEs were mild or moderate in severity**
- **No difference in PK exposure between Asian and non-Asian patients was observed**
  - **Increased neutropenia rate in Asian vs non-Asian patients may be attributed to low baseline ANC**
- **Palbociclib + fulvestrant may be a reasonable therapeutic option in Asian patients**

AE = adverse event; ANC = absolute neutrophil count; HR+ = hormone receptor positive; HER2– = human epidermal growth factor receptor 2 negative; MBC = metastatic breast cancer; PFS = progression-free survival; PK = pharmacokinetic
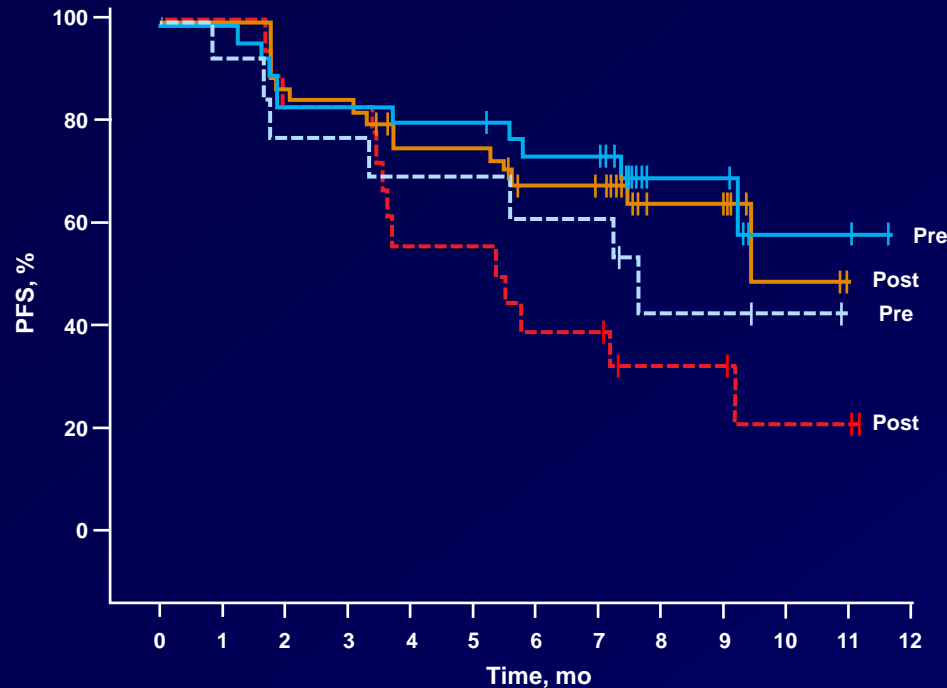
Acknowledgments

- **We thank all patients and investigators who participated in the PALOMA-3 study**

- **Pharmacokinetic data were kindly provided by Justin Hoffman and Yanke Yu of Pfizer Inc**

- **Editorial support for this presentation was provided by Anny Wu, PharmD, of Complete Healthcare Communications, LLC, and was funded by Pfizer Inc**

Backup Slides

Demographics and Baseline Disease Characteristics in Asian Cohort

Characteristic	Palbociclib + Fulvestrant (n=74)	Placebo + Fulvestrant (n=31)
Median (range) age, y	53 (34–82)	50 (39–79)
<65, n (%)	62 (84)	24 (77)
≥65, n (%)	12 (16)	7 (23)
Menopausal status		
Premenopausal or perimenopausal	31 (42)	13 (42)
Postmenopausal	43 (58)	18 (58)
Median (range) weight, kg	57 (36–83)	56 (35–71)
Median (range) height, cm	155 (140–167)	155 (145–174)
ECOG performance status, n (%)		
0	52 (70)	21 (68)
1	22 (30)	10 (32)
Measurable disease present, n (%)	58 (78)	29 (94)
Documented sensitivity to prior hormonal therapy, n (%)	58 (78)	26 (84)
Previous chemo regimen for primary diagnosis, n (%)	51 (69)	24 (77)
Previous hormonal regimen for primary diagnosis, n (%)		
1	22 (30)	11 (36)
>1	52 (70)	20 (65)
Prior tamoxifen, n (%)	54 (73)	23 (74)
Prior aromatase inhibitors, n (%)	54 (73)	24 (77)

ECOG = Eastern Cooperative Oncology Group

Premenopausal and Postmenopausal PFS in Asian Patients

HR = hazard ratio; PFS = progression-free survival
Date of data cut-off: March 16, 2015

Baseline ANC in Asian vs Non-Asian Patients

- **Lower baseline ANC was associated with Asian race, lower baseline ALT, and lower age**
- **Importantly, race was not found to be a covariate on any of the PK-ANC model PD response parameters, implying that there was no increased sensitivity to palbociclib-induced neutropenia within the Asian population**

	Asian (N=72)	Non-Asian (N=237)
Baseline ANC (x10^9/L)		
median (range)	2.91 (1.65-8.2)	3.6 (1.3-14.8)
arithmetic mean	3.17	3.94
geometric mean	3.01	3.68
Baseline ALT		
median (range)	17 (7-127)	21 (5-145)
arithmetic mean	22.7	25.7
geometric mean	18.3	21.7
Age (years)		
median (range)	52.5 (34-82)	58 (30-88)
arithmetic mean	52.5	58.0
geometric mean	52.6	56.8

Abbreviation: ALT=alanine aminotransferase, ANC=absolute neutrophil count, N=number of patients.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; PD = pharmacodynamic; PK = pharmacokinetic