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ESMO Asia
Discussant
Abstracts #530 and #550

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

Disclosures

Consulting or advisory role: AstraZeneca, Celgene, Novartis, Pfizer, Roche

Travel grants: Eisai, Roche, Merck

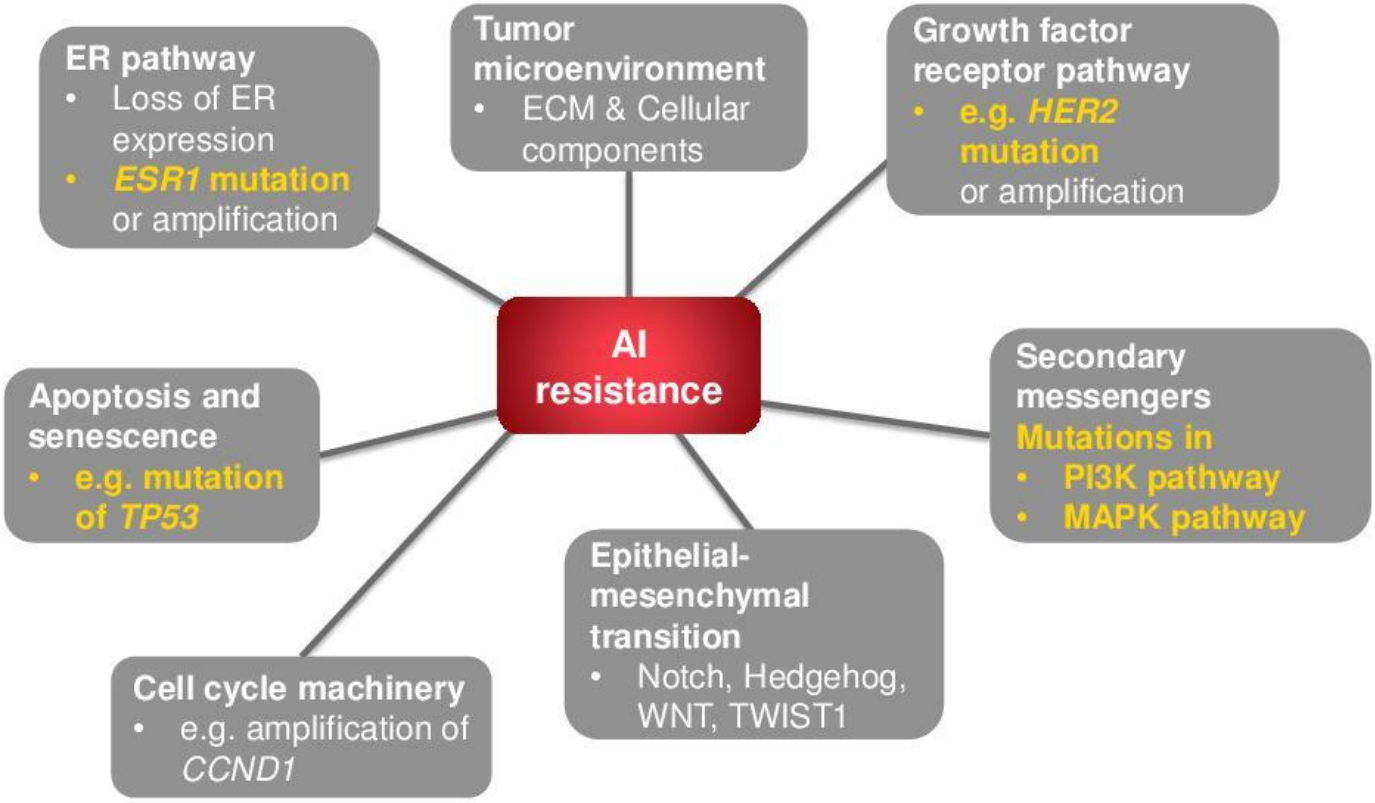
Abstract #530

Efficacy and safety of palbociclib plus fulvestrant in Asian women with hormone receptor positive (HR+)/human epidermal growth factor-2 negative (HER2-) metastatic breast cancer (MBC) that progressed on prior endocrine therapy (ET)

Au: Jungsil Ro, Korea

San Antonio Breast Cancer Symposium, December 8-12, 2015 ,Pascal Gellert

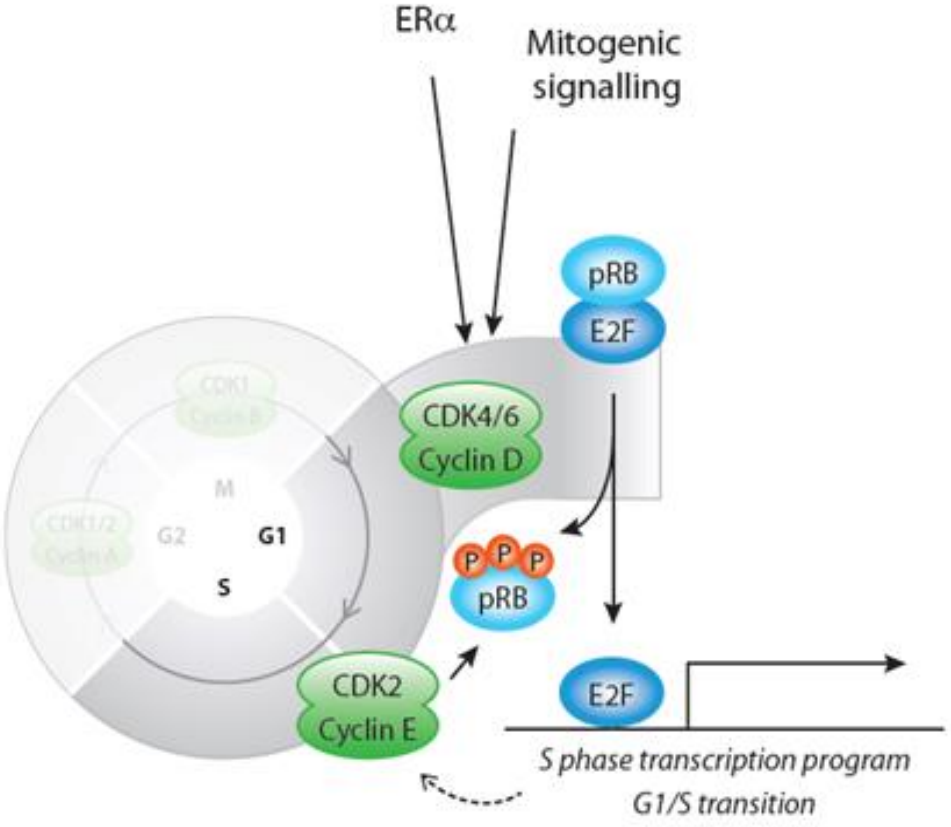
The Hallmarks of AI resistance



modified from Ma *et al*, Nature 2015

Endocrine Resistance and CDK Inhibition

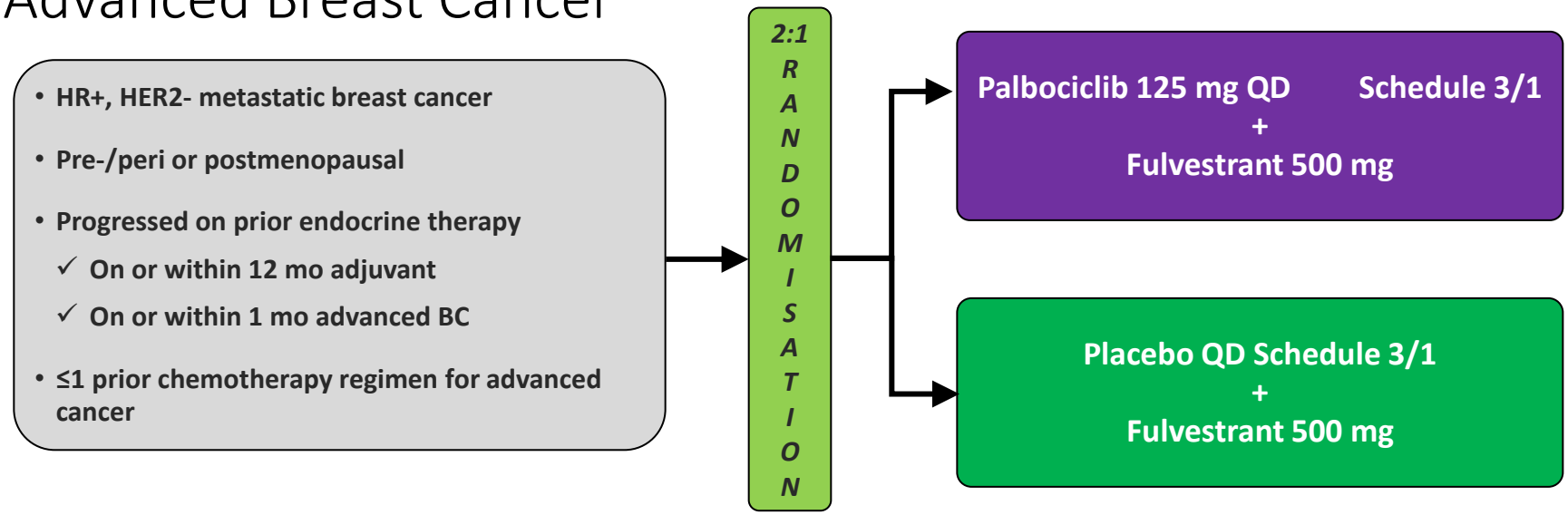
- Growth of HR+ BC is dependent release of E2F TF after P'n of Rb
- Cyclin D1 partnered with CDK 4/6 hence permit G1-S phase transition thru restriction point and cell cycle entry
- Endocrine resistant cell lines are dependent on hypoP'd Rb, Cyclin D1 amplification and p16 inhibition



Palbociclib

- Oral selective inhibitor of CDK 4/6
  - Inhibits cell proliferation, DNA synthesis by preventing cell-cycle progression from G1 to S phase; induces senesence
  - Active in cell line models of endocrine resistance and synergistic with anti-E2 strategies such as fulvestrant
- Paloma 1: phase II randomized trial of first line letrozole +/- palbociclib
  - Significant improvement in PFS with palbociclib (10 vs 20 mos, HR .488, p=.0004)
    - No improvement in OS (33.3 vs 37.5 mos)
  - Primary toxicity: asymptomatic neutropenia
  - Accelerated FDA approval 2/2015

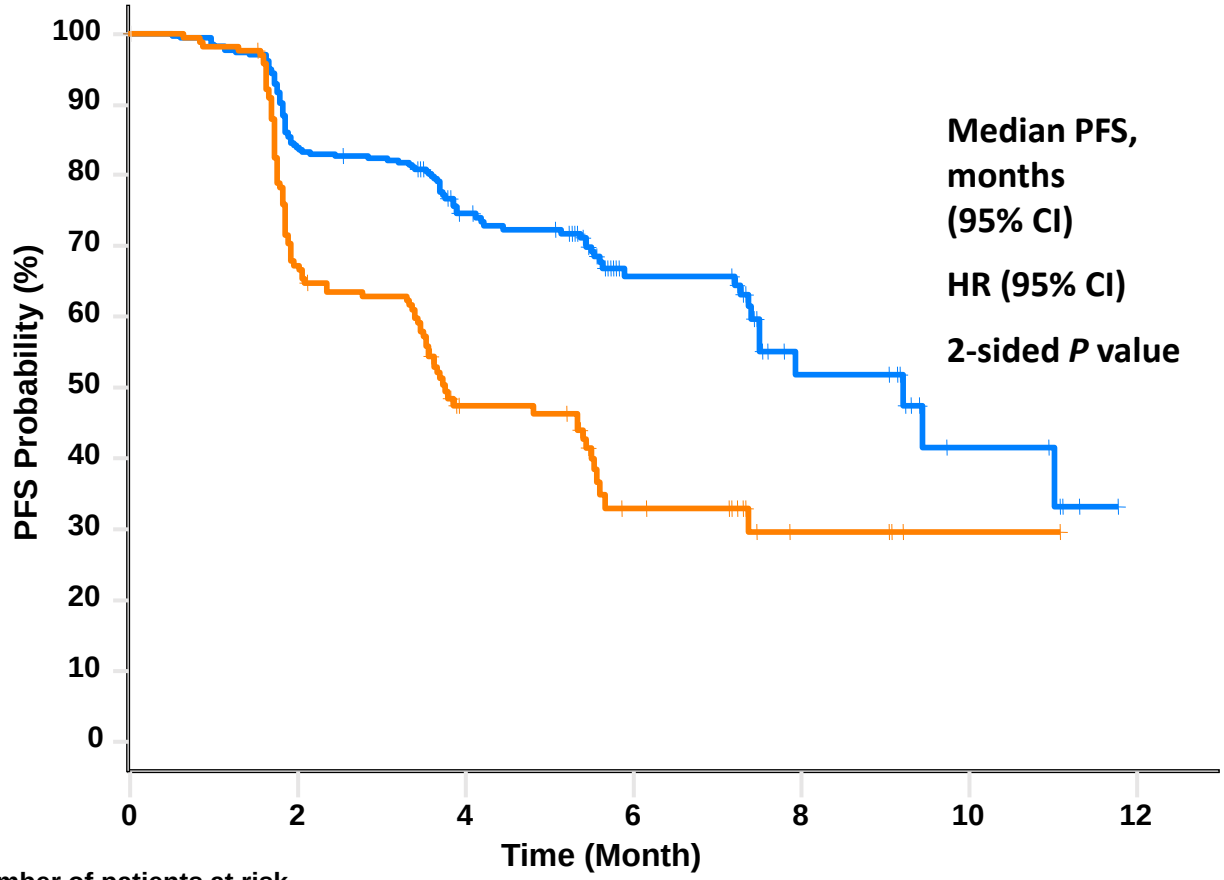
PALOMA 3: Randomised Phase 3 Trial in Endocrine-Resistant Advanced Breast Cancer



90% power to detect HR=0.64 for increase mPFS from 6 to 9.4 months

- **N=521 Multicenter, Double-blind, Placebo-controlled**
- **Primary Endpoint**: PFS by investigator assessment
- **Secondary Endpoints**: OS, OR, DR, CBR, PK (DDI), PRO, Biomarker, Safety
- **1-IA for efficacy:** Haybittle-Peto efficacy boundary (1-sided α =0.00135)
- **Stratification Factors**:
  - Menopausal status at study entry
  - Sensitivity to prior hormonal therapy
  - Presence of visceral disease

Primary Endpoint: PFS (ITT Population)

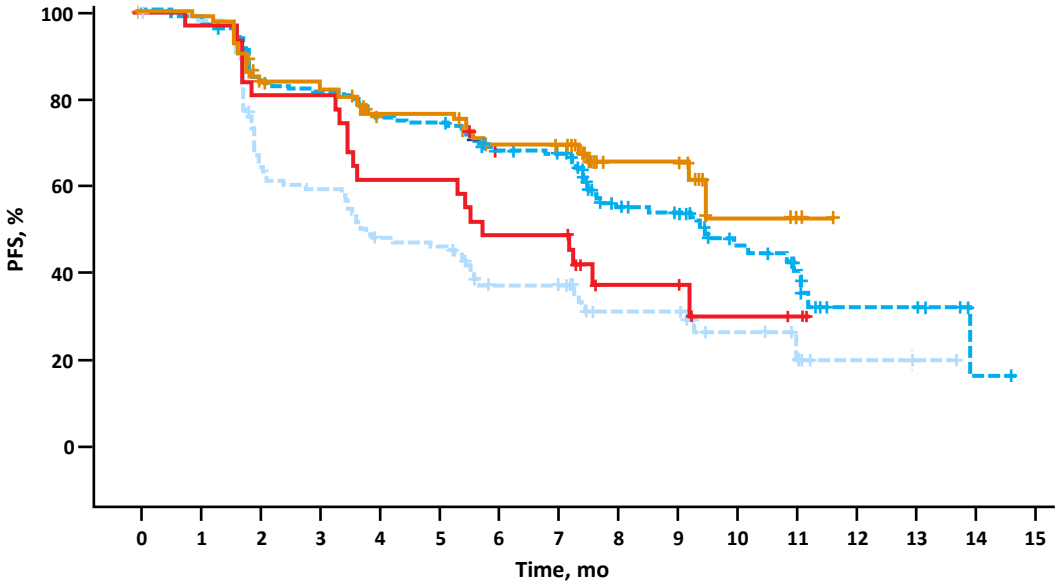


Number of patients at risk

PAL+FUL	347	279	132	59	16	6
PCB+FUL	174	109	42	16	6	1

	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided *P* value	<0.000001	

First Analysis of Efficacy in Asian Patients



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

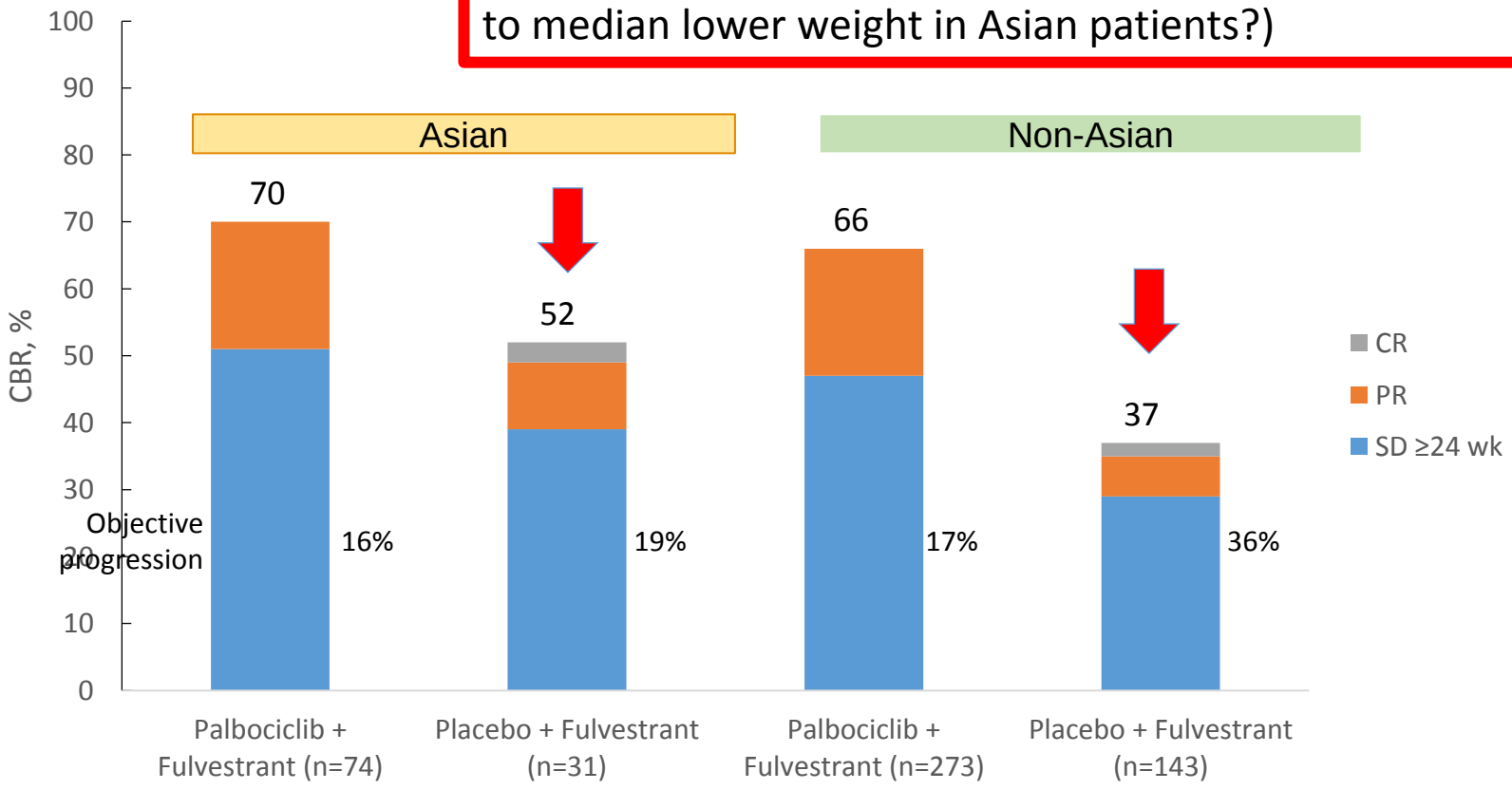
	Palbociclib + Fulvestrant n=273	Placebo + Fulvestrant n=143
HR (95% CI)	0.451 (0.343–0.593)	
1-sided *P* value	<0.0001	

Similar Benefit in PFS of Palbociclib between Asian and Non-Asian Patients
HR 0.48 vs. 0.45

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

Secondary Endpoints: Response Assessment

Control of arm of Fulvestrant:
Higher Response in Asian 52% vs. 37% non-Asians
(may just be due to small sample size or possibly due to median lower weight in Asian patients?)



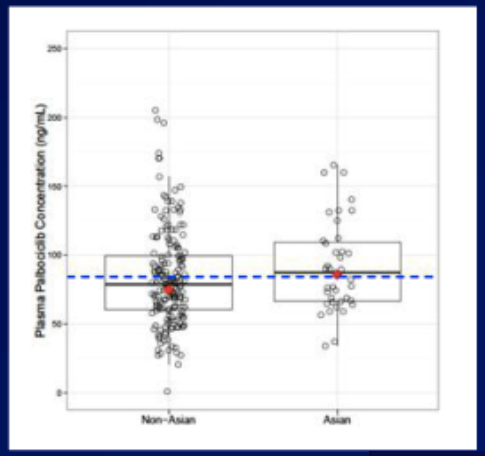
Asian vs. Non-Asian patients

	Asian (n=105)	Non-Asian (n=416)
Demographics:		
• **Premenopausal/perimenopausal**	42%	15%
• **Median (range) weight, kg**	56kg (35-83)	72kg (43- 142)
AE – All grades (Palbo + Fulvestrant)		
• **Neutropenia**	67 (92%)	212 (78%)
• **Stomatitis**	19 (26%)	24 (9%)
• **Rash**	18 (25%)	17 (6%)
• **Nasopharyngitis**	15 (21%)	26 (10%)
• **Fatigue**	14 (19%)	121 (45%)
Febrile Neutropenia	4% (Palbo + Fulvestrant) (3/73 patients) 2 reported as SAEs	Not reported (0.6% from all patients, NEJM Turner et al. 2015)

Real or Body Surface Area Differences?

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 m
open circles represent individual patient values. Dashed
represents the arithmetic mean value of all data from all
Box plot provides median and 25%/75% quartiles with w
point within 1.5 times interquartile range

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

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

Inter-Ethnic Differences—How Important is it in Cancer Treatment?

Winnie HY Ling,[1] *MBBS, MRCP*, Soo Chin Lee,[1] *MBBS, MRCP, MMed (Int Med)*

Table 1. Inter-ethnic Difference in Drug Response and Implicated Genes

Drug	Clinical Effects	Implicated Gene
Warfarin	Asians require lower dose.	*VKORC1*
Doxorubicin	Asians experience more myelosuppression.	*CBR3*
Docetaxel	Asians have reduced clearance and experience more myelosuppression.	-
5-Fluoropyrimidines	Asians are less likely to have gastrointestinal toxicities.	*TYMS* (possible role)
Gefitinib	Asians are more likely to have treatment response. Japanese are more susceptible to develop interstitial pneumonitis.	EGFR activating mutations
Tamoxifen		*CYP2D6* (inter-ethnic difference in metabolizer genotypes and phenotypes)

Pharmacogenomics: CYP2D6 and Metabolism of Tamoxifen

Tamoxifen is widely used as endocrine therapy for hormone-receptor positive breast cancer

- its clinical effects rely on efficient conversion to 4-hydroxytamoxifen (4-OH-tam) and endoxifen by the cytochrome P450 2D6 (*CYP2D6*) enzyme

Tamoxifen can likely take credit for saving more patient's lives than any other cancer drug currently available

- a great deal is unknown about who benefits and why

DFS

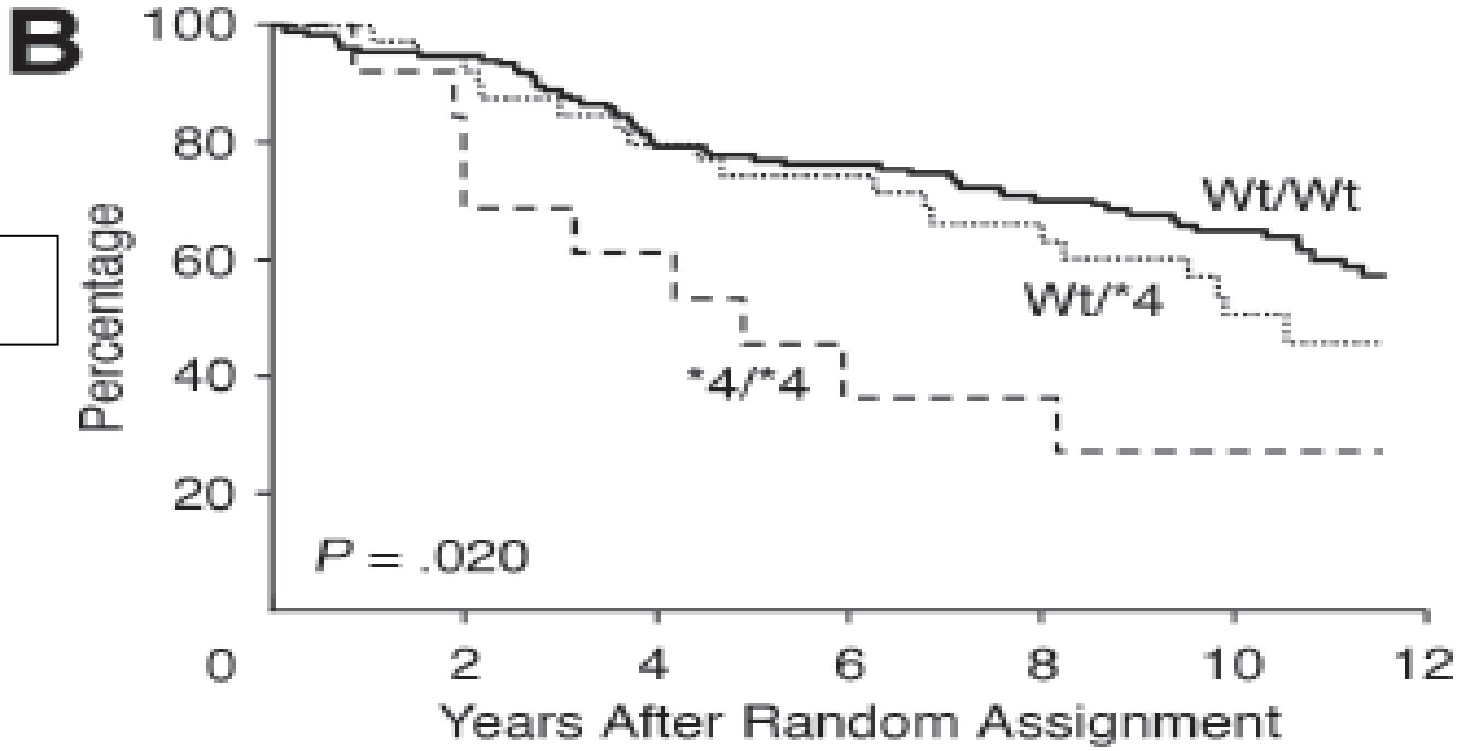


Table 2. Interethnic allele frequencies of selected tamoxifen drug-metabolizing enzymes

Genetic variant	Allele frequencies (%)	
	Caucasians	Asians
*CYP2D6*3* (11)	1-2	0
*CYP2D6*4* (11)	12-30 (median, 20%)	1-2
*CYP2D6*5* (11)	2-7	4-6
*CYP2D6*6* (11)	1	0
*CYP2D6*10* (11)	1-2	38-70 (median, 41%)
*CYP2D6*17* (11)	<1	<1
*CYP2D6*41* (30)	8-10	0-2
*CYP2D6*2xn* (115)	1-5	0-2
*CYP3A4*1B* (71)	2-9.6	0
*CYP3A5*3C* (116)	88	75
*SULT1A1*2* (117, 118)	33	0-8

North Central Cancer Treatment Group
Paraffin-embedded samples (n=223)

Tan et al. Clin Cancer Res 2008 , 14(24): 8027-41

Doxorubicin: Asians vs Caucasians

Toxicities		NSABP B-15 ($n = 1462$) (patient %)	PWH ($n = 85$) (patient % (95% CI))
Neutropenia	Grade 3	3.4	52 (41, 63)
	Grade 4	0.3	25 (16, 35)
Thrombocytopenia	Grade 3	0	0
	Grade 4	0.1	0
Fever	Moderate to severe	5.5	5.9 (2, 14)
	Death	0	0
Vomiting	Grade 1–2	71.2	52.9 (42, 64)
	Grade 3–4	4.7	12.9 (7, 22)
Mucositis	Grade 1–2	Not stated[b]	12.9 (7, 22)
	Grade 3–4		0
Diarrhoea	Grade 1–3	2.6	3.5 (1, 11)
	Grade 4	0.3	
Liver (hepatitis: alanine transaminase)	Grade 1–2	Not reported	
	Grade 3–4	Not reported	
Acute cardiac toxicity		0	

Ma et al. Radiother Oncol 2002; 62: 185

Retrospective study
HK Chinese treated with doxorubicin/CTX vs Caucasians treated on NSABP protocol
Gd 3/4 neutropenia:
77% (Asians) vs 3.7% (Caucasians)

Doxorubicin-induced myelosuppression

	Doxorubicin-induced myelosuppression (percentage difference from baseline, %)	
	Nadir total white	*Nadir neutrophil*
Chinese ($n = 66$)	75 ± 12	92 ± 10
Malay ($n = 26$)	66 ± 14	87 ± 10
Indian ($n = 7$)	60 ± 21	80 ± 14
	$P^a = 0.003$	$P = 0.010$
	$P^b = 0.024$ Chinese versus Malay	
	$P^b = 0.025$ Chinese versus Indian	$P = 0.021$ Chinese versus Indian

Degree of neutrophil suppression:
Chinese>Malays>Indians

Hor et al. Pharmacogenomics J 2008; 8: 139

Docetaxel: Asians have higher neutropenia and febrile neutropenia rates

- **Asians have higher reported febrile neutropenia rates** compared to Caucasians
  - Differing starting doses: Caucasians docetaxel 100mg/m^2, China/Korea/Singapore 70-75mg/m^2, Japan docetaxel 60mg/m^2

- Possibly due to differences in **drug clearance**

- PK and PD of docetaxel 75mg/m^2 (n=24) or 100mg/m^2 (n=8) studied in 32 patients from NUH (majority NSCLC, 3 breast patients)
  - **Clearance was about 30% lower** while **drug exposure (AUC) was about 25% higher in Asians** compared to reported data in Caucasians
  - Febrile neutropenia rates 29%
  - No definite genetic etiology identified

Goh et al. JCO 2002; 20: 3683

CLEOPATRA: Exposure to docetaxel in patients from Asia

Docetaxel dose reductions below 75 mg/m2 occurred in 47% of patients from Asia compared with13% of patients from other regions.

But did not adversely affect efficacy in patients from Asia, with PFS and overall survival being comparable with that of patients from other regions.

A reduction in the docetaxel starting dose should therefore be considered in patients from Asia…

				PHT n = 125
Median				20.0 (1–50)
Median				9.0 (1–30)
Median				23.9
Docetax				1 (0.8)
Docet (%)				62 (49.6)
One				61 (48.8)
Two				1 (0.8)
Docetax				
No, n (%)	97 (36.1)	78 (27.7)	45 (35.2)	31 (24.8)
Yes, n (%)	172 (63.9)	204 (72.3)	83 (64.8)	94 (75.2)
	166/172 (96.5)	194/204 (95.1)	79/83 (95.2)	91/94 (96.8)

Data cut-off: May 2011

* Includes patients with initial dose escalation to 100 mg/m^2 followed by two subsequent dose reductions

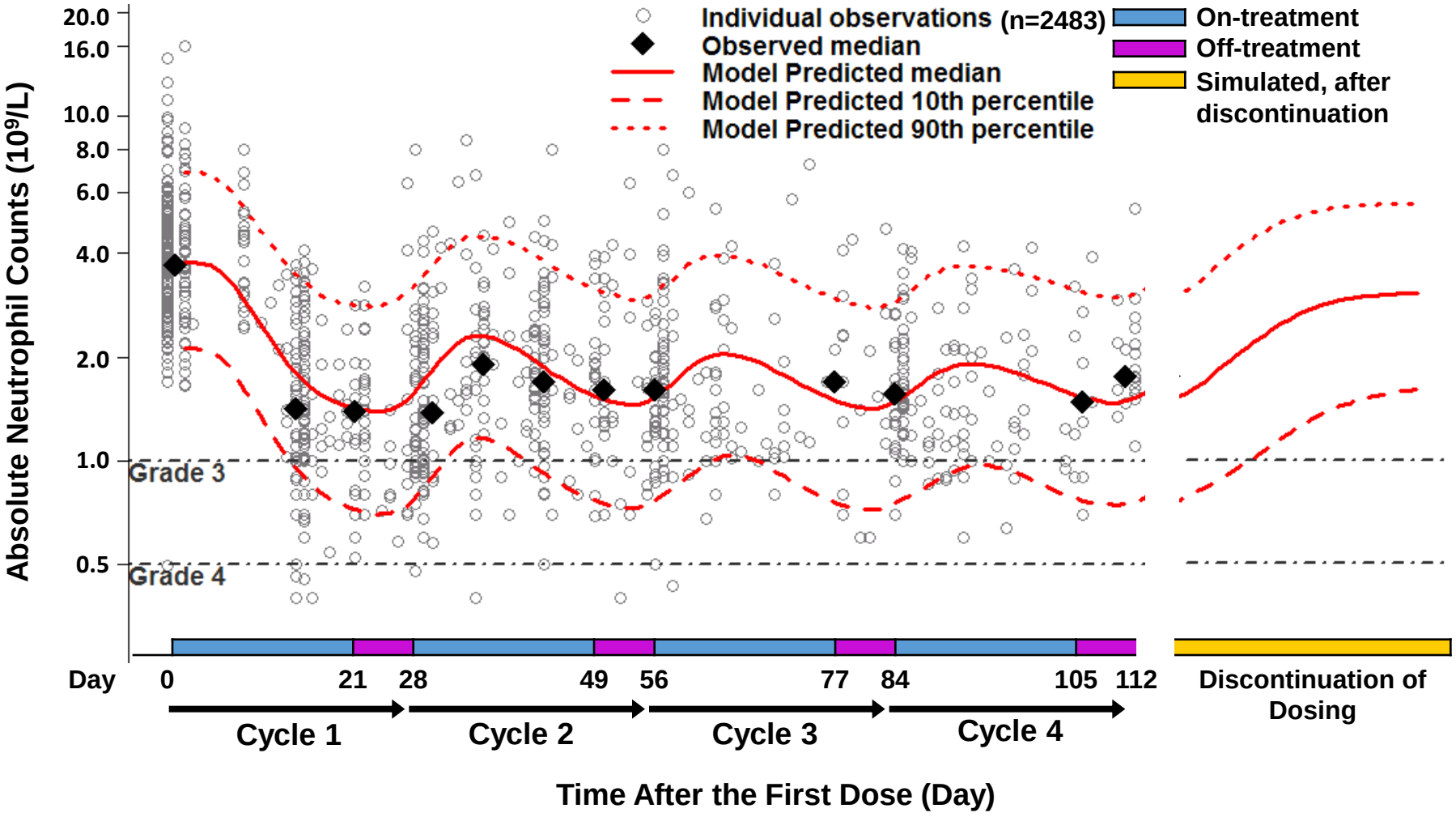
H, trastuzumab; P, pertuzumab; T, docetaxel

Swain SM, *et al*. *The Oncologist* 2014; **19**:1–9

Impact of Toxicity

- These toxicities led to dose reductions and delays
- Small numbers – but little reporting yet of breakdown of grade3-4 toxicities
- Baseline ANC lower, but median of 2 patients in Asian and non-Asian patients hence interruptions and delays must be due to a subset of patients with either baseline lower ANC levels or heightened sensitivity to Palbociclib
- 4% risk of febrile neutropenia vs 0.6% from NEJM Paloma 3 publication
  - may be due to differences in pharmacogenomics

Observed and Model Predicted Neutrophil Over Time Profile



Includes data from Study 1001, 1002, 1003

Guidelines and recommendation for monitoring

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
WBC count decreased (leukopenia)	<LLN–3,000/mm³; <LLN–3.0x10⁹/L	<3,000–2,000/mm³; <3.0–2.0x10⁹/L	<2,000–1,000/mm³; <2.0–1.0x10⁹/L	<1,000/mm³; <1.0x10⁹/L	–
Neutrophil count decreased (neutropenia)	<LLN–1,500/mm³; <LLN–1.5x10⁹/L	<1,500–1,000/mm³; <1.5–1.0x10⁹/L	<1,000–500/mm³; <1.0–0.5x10⁹/L	<500/mm³; <0.5x10⁹/L	–
Febrile neutropenia[b]	–	–	ANC <1,000/mm³ + single temperature of >38.3°C or sustained temperature of ≥38°C for >1 hour	Life-threatening consequences;[c] urgent intervention indicated	Death

WBC growth factor use	Recommendation
Primary prophylaxis	Not permitted
Treatment of treatment-emergent neutropenia	As indicated by ASCO guidelines[b]
Secondary prophylaxis	If neutropenic complications are observed in a cycle during which primary prophylaxis with WBC growth factors was not used, secondary prophylaxis is permitted in subsequent cycles at the discretion of the investigator, providing dose reduction or dose delay is not a reasonable alternative

---------- WARNINGS AND PRECAUTIONS ----------

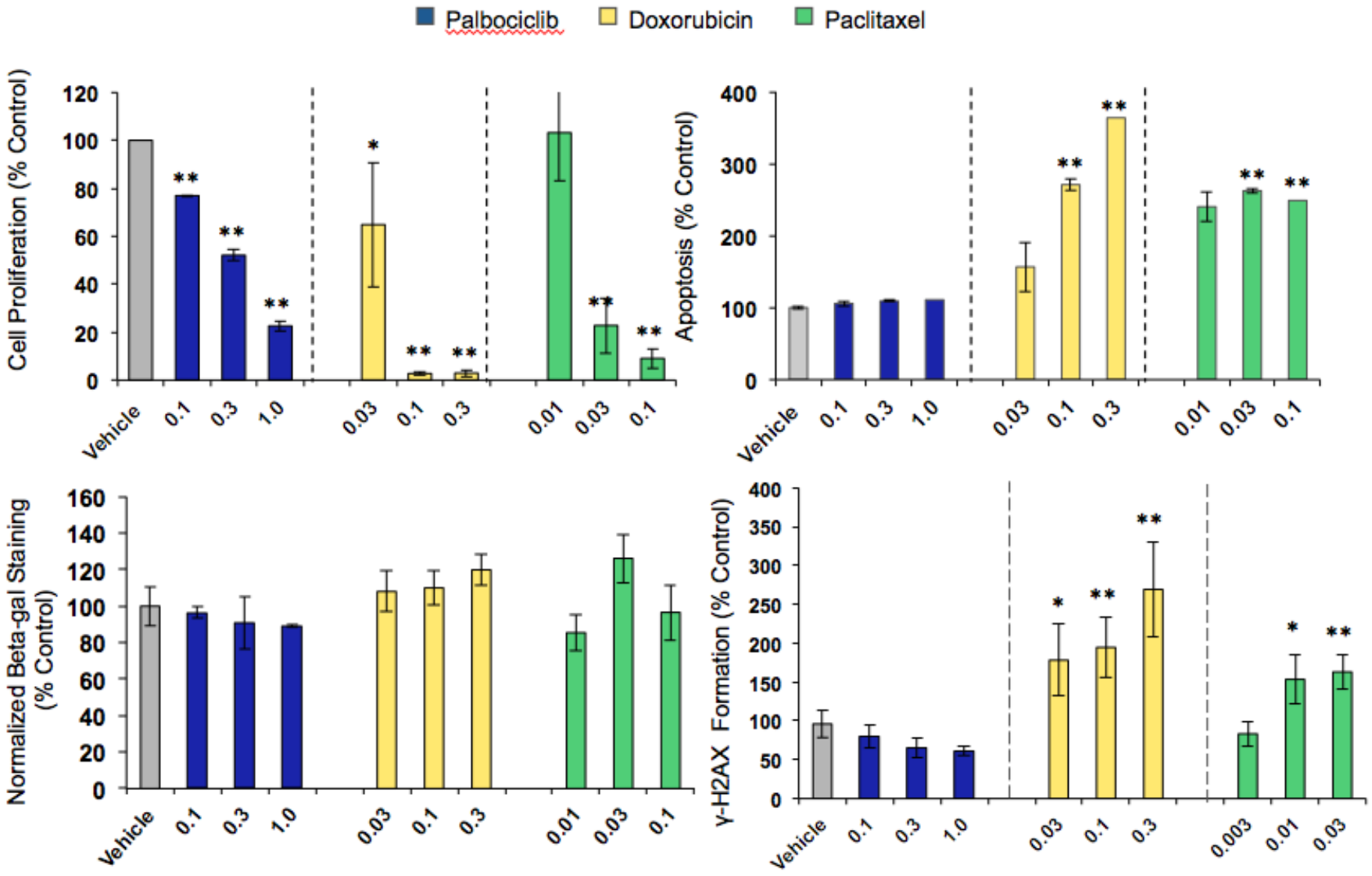
- Hematologic: Neutropenia may occur. Monitor complete blood count prior to start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first two cycles, and as clinically indicated. (5.1)
- Infections: Monitor for signs and symptoms and withhold dosing as appropriate. (5.2)

Table 12. Management of palbociclib-associated neutropenia:[a] dose reductions.

Toxicity	Recommended palbociclib dose modification
Grade 1 or 2 (ANC ≥1,000/mm³)	No dose adjustment is required
Uncomplicated grade 3 neutropenia (ANC 500–<1,000/mm³)	No dose adjustment is required Consider repeating CBC monitoring 1 week later Withhold initiation of next cycle until recovery to grade ≤2
Grade 3 neutropenia (ANC <1,000/mm³) associated with a documented infection or fever ≥38.5°C	Withhold palbociclib and initiation of next cycle until recovery to grade ≤2 Resume treatment at next lower dose
Grade 4 neutropenia (ANC <500/mm³)	Withhold palbociclib and initiation of next cycle until recovery to grade ≤2 Resume treatment at next lower dose

[a]Monitor CBC prior to the start of palbociclib therapy and at the beginning of each cycle, as well as on day 14 of the first two cycles, and as clinically indicated.

Fig. 1 In Human Bone Marrow Cells: Palbociclib Caused Cell Cycle Arrest, but Not Apoptosis or DNA-Damage Compared to Cytotoxic Chemotherapy



*p<0.05; **p<0.01, ANOVA

Comparison of CDK 4/6 inhibitors

	Palbociclib				Ribociclib	Abemaciclib2	
	Letrozole combo, ph2, Hormone sensitive[1] (N=165)		With fulvestrant, ph3, Hormone refractory[2] (n= 521)		Single agent, FIH ph1, solid (N=132)	Single agent, ph1, refractory mBC (N=36)	
Efficacy	PFS : 20.2m vs 10.2m RR : 43% vs 33% CBR : 81% vs 58%		PFS : 9.5 m vs 4.6 m RR : 19.0% vs 8.6% CBR : 66.6% vs 39.7%		No MBC data	PFS 8.8 months RR 33.3% CBR 61.1%	
Safety – hematologic	All Neutro 75% Leuko 43% Anemia 35% Thrombo 17%	Grade ¾ Neutro 54% Lekco 19% Anemia 6% Thrombo 2%	All Neutro 79% Leuko 46% Anemia 26% Thrombo 19%	Grade ¾ Neutro 62% Leuko 26% Anemia 3% Thrombo 2%	All Neutro 40% Leuko 36%	All Neutropenia 40%, Leukopenia 32% Anemia 19% Thrombocytopenia 32%	
Safety - non-hematologic	All Fatigue 41% Diarrhea 20% Nausea 25%	Grade ¾ Fatigue 5% Diarrhea 4% Nausea 2%	All Fatigue 38% Nausea 29% Diarrhea 19%	Grade ¾ Fatigue 2% Nausea 0% Diarrhea 0%	All Nausea 35% Fatigue 27% QTc prolong	All Diarrhea 68%, Nausea 60%, Fatigue 45%, Vomiting 45%	Grade ¾ Diarrhea 9%, nausea 4%

1. Finn RS et al, PALOMA 1: CDK4/6 inhibitors palbociclib in combination with letrozol, Lancet Oncol, 2015; 16: 25-35.
2. Christofanill M et al, PALOMA 3 : Confirmed efficacy and safety. Presented at SABCS 2015; TX. Abstract
3. Infante IR et al, Phase 1 study of the single-agent CDK4/6 inhibitor LEE011 in pts with advanced solid tumors and lymphoma, JCO 2014:32(supple):2528a
4. Tolaney SM et al, Clinical activity of abemaciclib, an oral cell cycle inhibitor in metastatic breast cancer. Presented at SABCS 2014; TX. Abstract P5-19-13.

Conclusions:

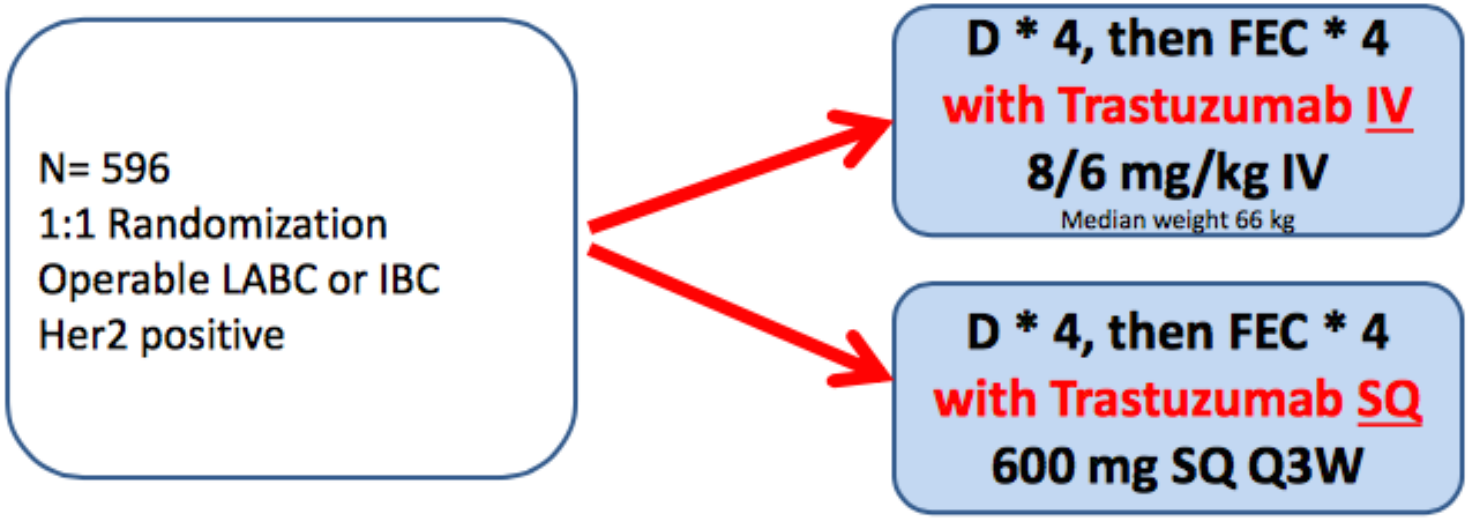
- Exciting first in class activity with accelerated approval for Palbociclib in Combination with Fulvestrant by FDA
- Early indications of small differences in toxicity between Asian and non-Asian pts whilst maintaining efficacy
- Increased neutropenia is assoc'd with a variety of factors?
  - differences in body wt, curface area and/or pharmacogenomics
- Opportunity for prospective trial
  - Omic, pG, efficacy, safety

Abstract #550

Phase III HannaH study of subcutaneous or intravenous trastuzumab for HER2-positive early breast cancer: Exploratory subgroup analyses of pathologic complete response and 3-year event-free survival by body weight and anti-drug antibody status

Au: Jin-Seok Ahn

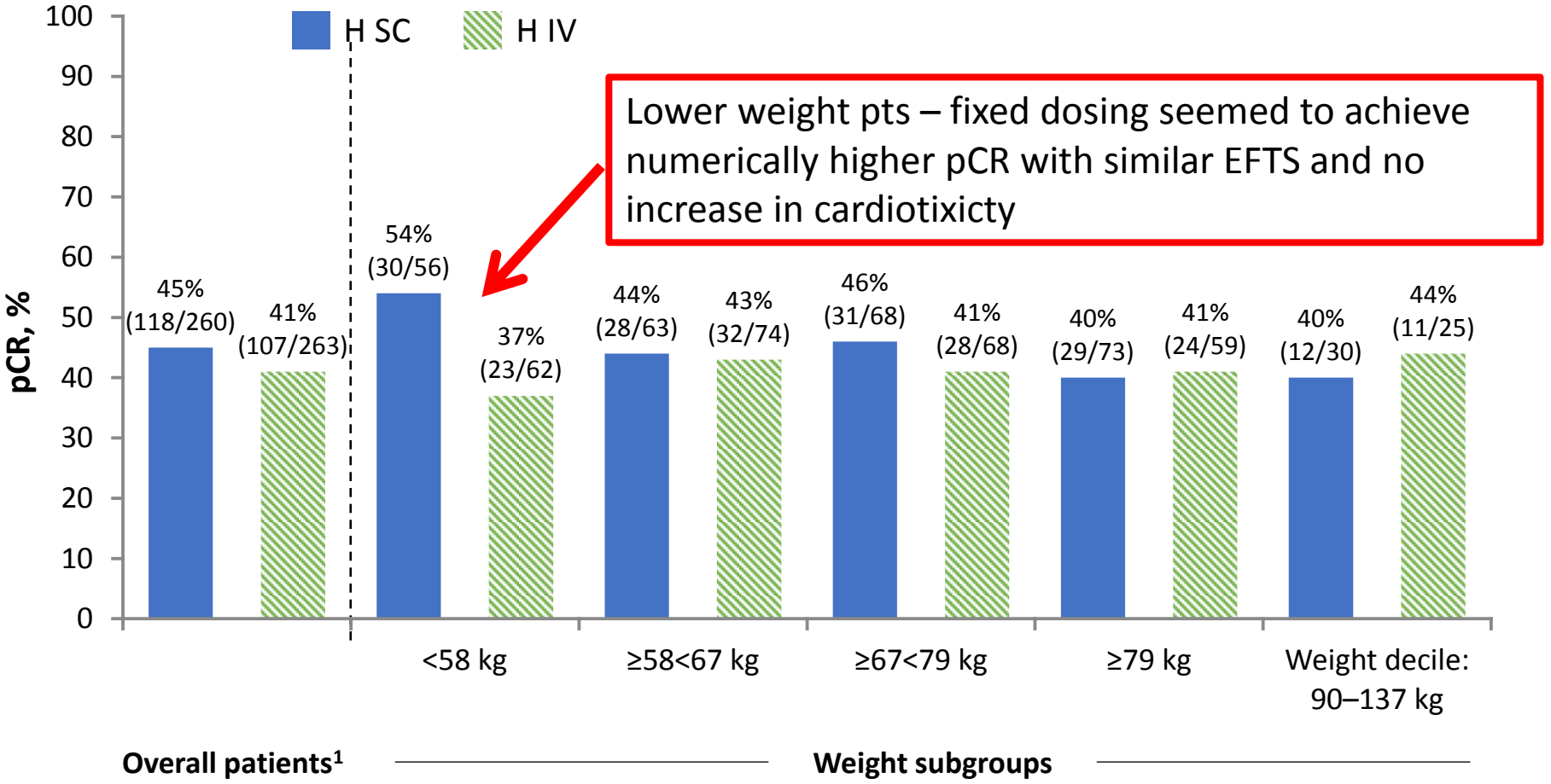
HannaH: Randomized NeoAdjuvant Phase III Trial Evaluating SubQ vs IV Trastuzumab



Docetaxel 75 mg/m2 IV Q3W * 4
Then FEC (500/75/500) Q3W * 4
+/- Trastuzumab during treatment
To be followed to complete a year of trastuzumab for 1 year

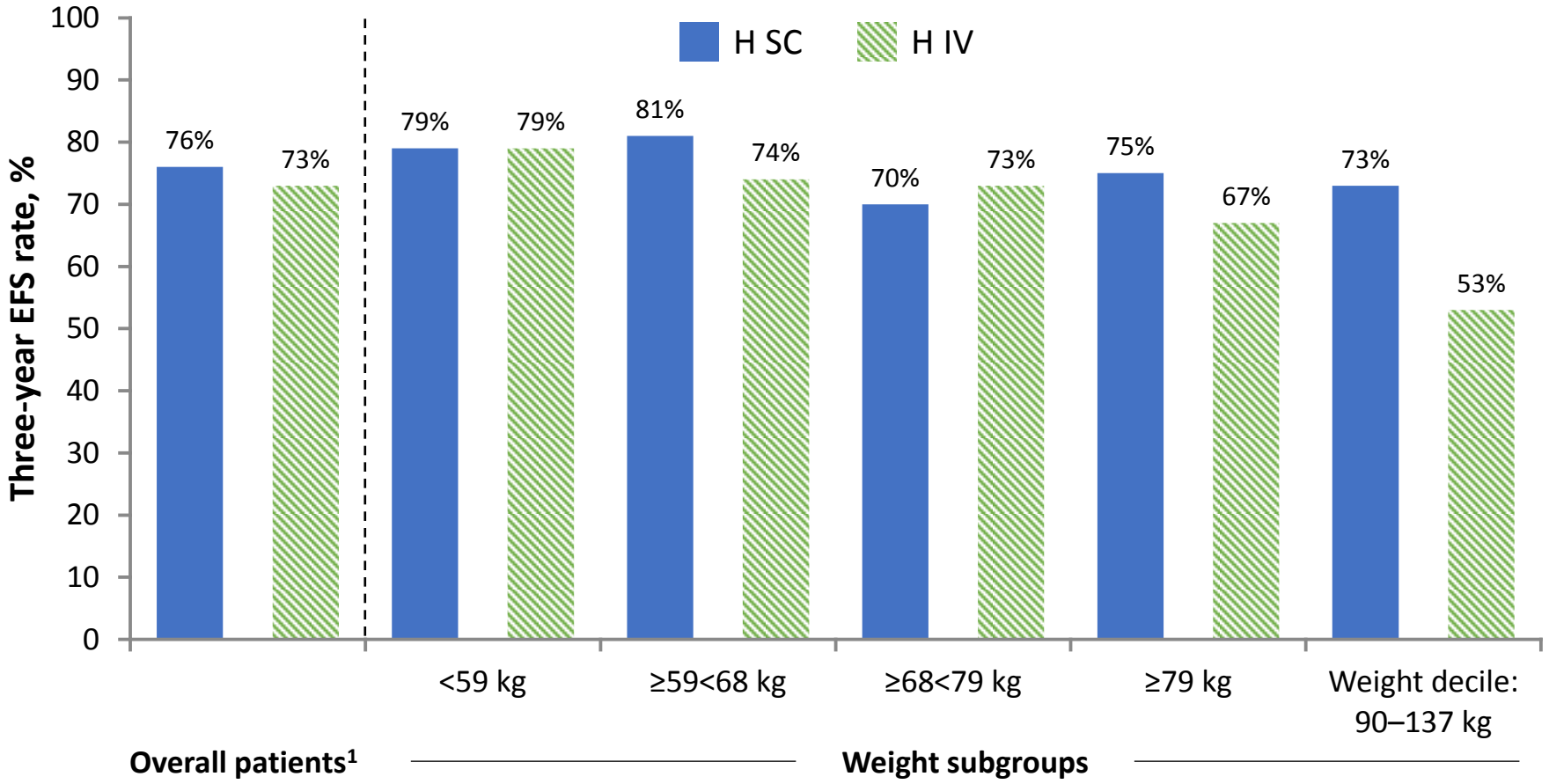
Ismael, G. et al. *Lancet Oncology August 9, 2012 vol. 13 ; 869 - 78*

HannaH: Efficacy (pCR) of fixed-dose H SC comparable to weight-based H IV overall and across weight subgroups (EPP population)



1. Ismael G, *et al*. *Lancet Oncol* 2012; 13: 869–878.

HannaH: Efficacy (3-year EFS) of fixed-dose H SC comparable to weight-based H IV overall and across weight subgroups (ITT population)



1. Jackisch C, *et al.* St. Gallen 2015; Poster P201.

HannaH: Study patients in each weight subgroup

Population	Overall patients[1]		Weight quartiles, kg								Weight decile, kg	
			ITT <59 EPP <58		ITT ≥59<68 EPP ≥58<67		ITT ≥68<79 EPP ≥67<79		ITT/EPP ≥79		ITT/EPP 90–137	
	H SC	H IV	H SC	H IV	H SC	H IV	H SC	H IV	H SC	H IV	H SC	H IV
ITT	294	297	71	77	70	83	71	70	82	67	34	29
EPP	260	263	56	62	63	74	68	68	73	59	30	25

1. Ismael G, *et al*. *Lancet Oncol* 2012; 13: 869–878.

Pertuzumab is administered using a fixed dosing scheme

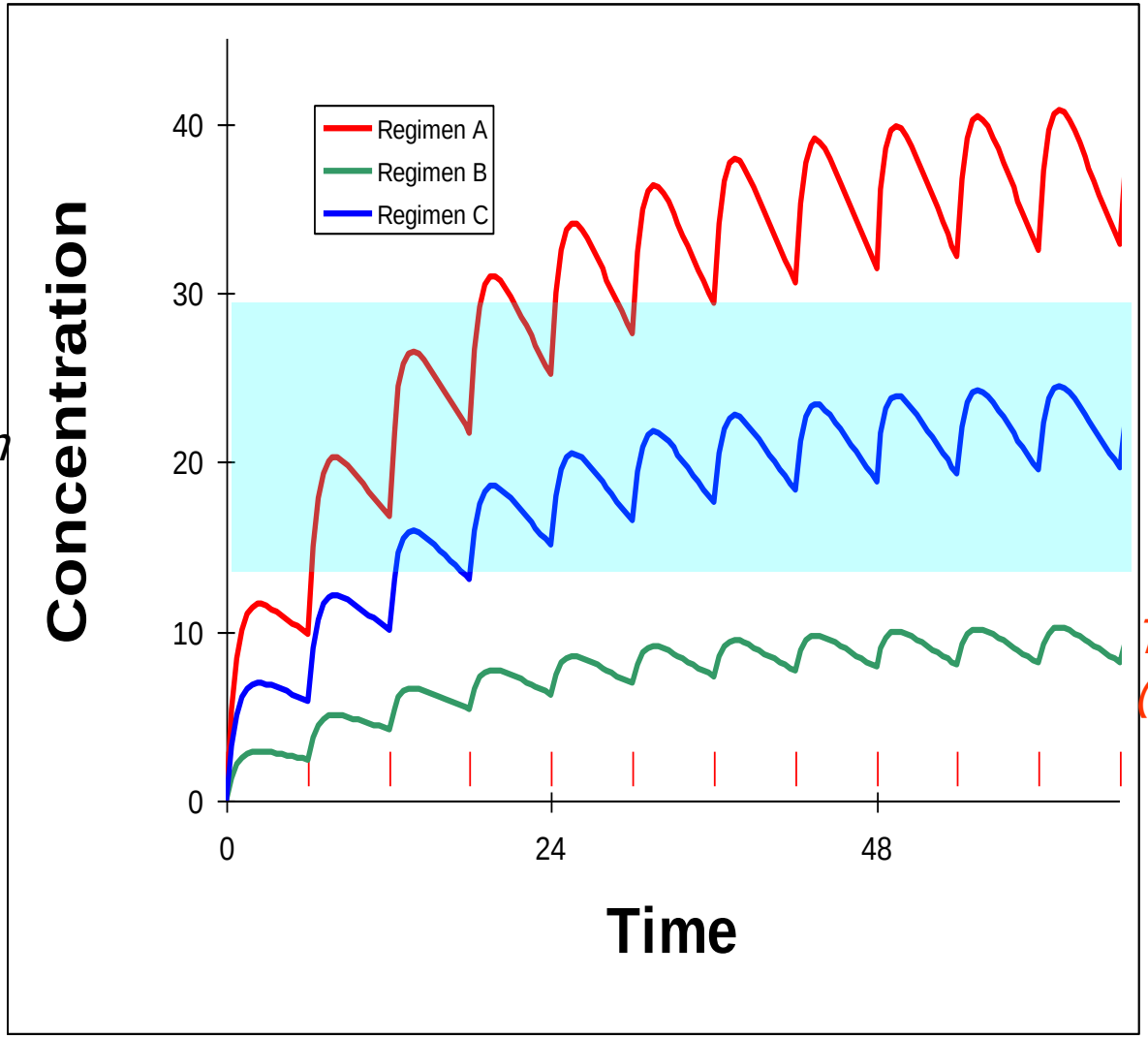
Pharmaceutical Research (© 2006)
DOI: 10.1007/s11095-006-0205-x

Rationale for Fixed Dosing of Pertuzumab in Cancer Patients Based on Population Pharmacokinetic Analysis

Chee M. Ng,[1,4] Bert L. Lum,[1] Veronica Gimenez,[2] Steve Kelsey,[3] and David Allison[1]

The Goal: To achieve an optimal dose and dosing regimen

Therapeutic Concentration Range

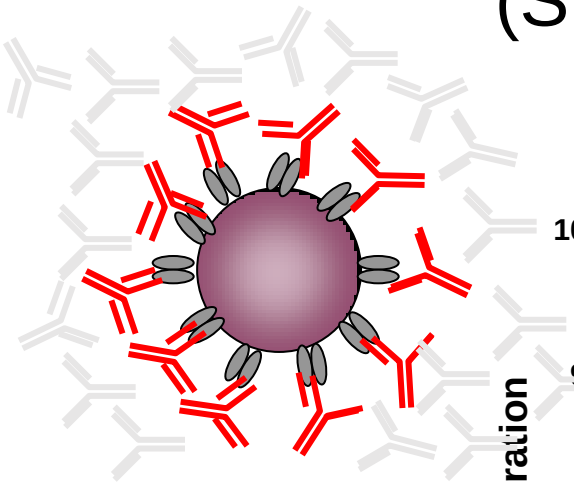


Therapeutic Failure (Safety/COGS)

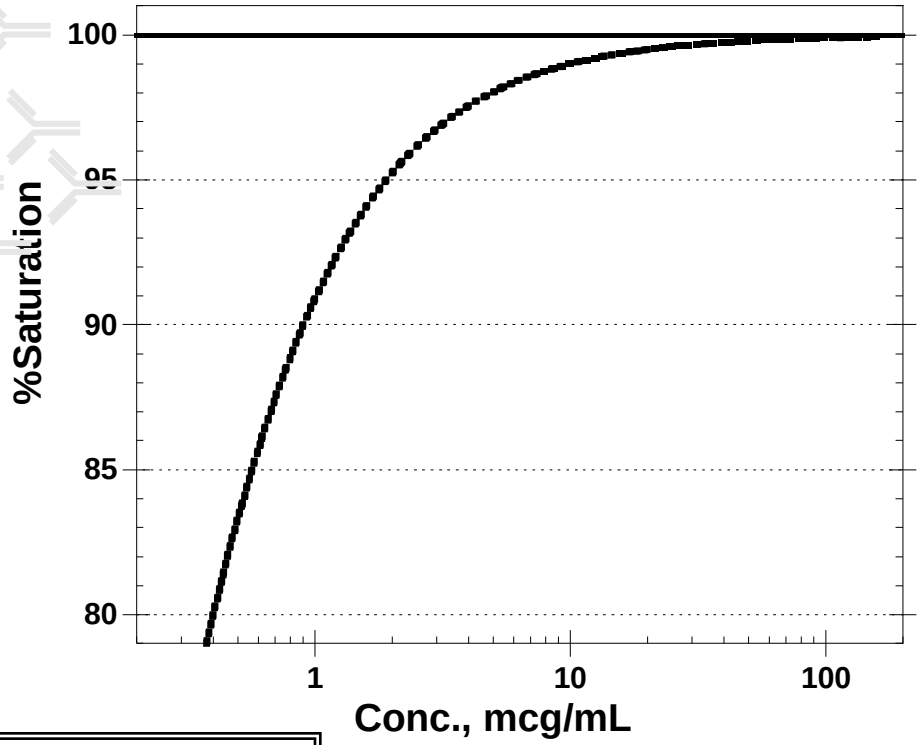
SUCCESS

Therapeutic Failure (Efficacy/Response)

rhuMAb IgG---Receptor Binding and Saturation (Simplified Law of Mass Action)



Ab + Receptor $\underset{K_{off}}{\overset{K_{on}}{\rightleftharpoons}}$ **Ab-Receptor**



Binding Affinity

$K_D = K_{off}/K_{on}$

K_D of Ab <1nM

(~ 0.1 ug/mL)

Emax Model

↑[Ab] ⇨ ⬆%Sat

20 ug/mL ~99.5%

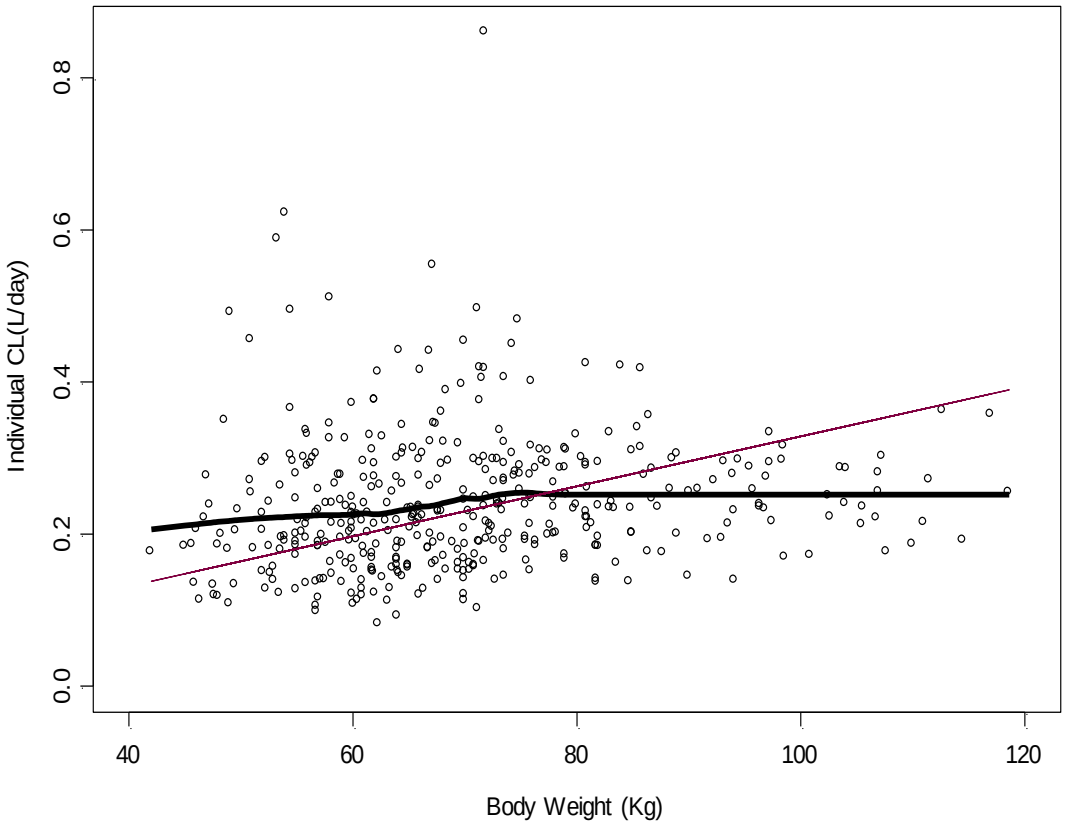
50 ug/mL ~99.8%

100 ug/mL ~99.9%

150 ug/mL ~99.93%

$$\%Sat = \frac{[Ab]}{[Ab] + K_D} \ (x100)$$

No significant trend in Trastuzumab CL when compared to body weight

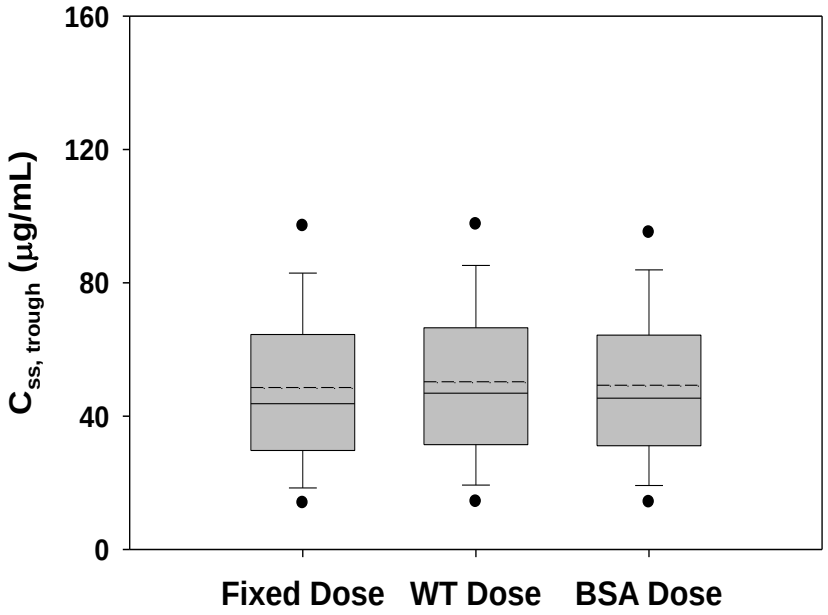


- Herceptin CL vs. BW
  - Trendline (red) represents the proportional relationship of CL versus weight (CL=0.23*Wt/70)

Clinical studies used for PK analysis

Study	Phase	Indication/design	Doses/regimens	No. of pts
TOC2297g	I	Advanced solid tumors	0.5, 2.0, 5.0, 10.0, and 15 mg/kg	18
BO16934	II	Metastatic breast cancer (MBC)	Arm A: 420 mg (840 mg loading dose) Arm B; 1050 mg	75
TOC2689g	II	Advanced ovarian cancer	Cohort I: 420 mg (840 mg loading dose) Cohort 2: 1050 mg	123
TOC2682g	II	Hormone refractory prostate cancer (HRPC) pretreated with docetaxel	420 mg (840 mg loading dose)	41
TOC2572g	II	Advanced, recurrent NSCLC	420 mg (840 mg loading dose)	43

Fixed, Weight-, or BSA-Based Dose:
equivalent exposure across entire population



$C_{ss,trough}$ (µg/mL)	Fixed Dose	WT-Based Dose	BSA-Based Dose
5th %-tile	14.0	14.4	14.3
Median	43.7	46.9	45.4
95th %-tile	96.6	97.4	94.6
%Patients < 20 µg/mL	12.0	10.8	10.9

Conclusions

- SC administration delivered over 5 minutes has a similar PK profile and appears to be as efficacious as IV but with added convenience of SC injection
  - reduced chemotherapy chair time and travel time
- In light of dual blockade in 1st line setting for mets disease with pertuzumab, may be equally convenient to give both IV infusions until SC formations available for both antibodies
- Reasonable strategy for adjuvant patients to be given maintenance SC herceptin

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