

Pharmacoethnicity and its impact on treatment

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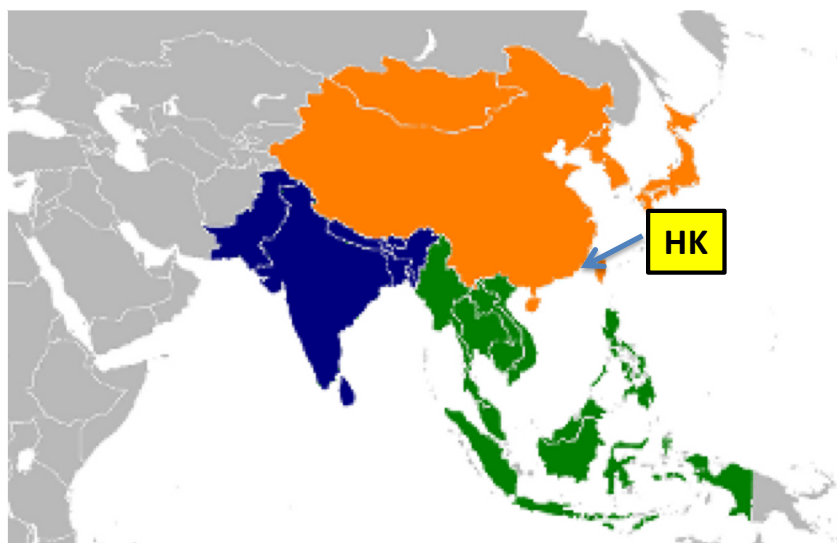
Disclosure

- Advisory board: Janssen, Ipsen, Astellas
- Speaker honorarium: Roche, BMS, Merck, Pfizer, MSD, Ferrings



Asian Ethnicity

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- east asia
- south asia
- southeast asia

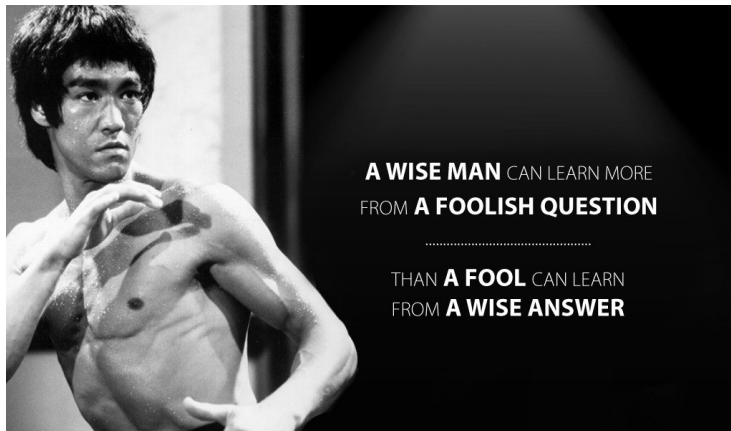
East Asian Ethnicity

Major countries/areas: **China** (including Hong Kong, Macau), **Japan**, Mongolia, North Korea, South **Korea**, and Taiwan.

Major ethnic groups : **Han, Korean, and Yamato**

Others: Bai, Hui, Tibetans, Manchus, Ryukyuan, Ainu, Zhuang, and Mongols

Hong Kong Icon: **Bruce Lee** (1940-1973)



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Taxane related-adverse event in Asian PCa patients



	mHSPC	mHSPC	mCRPC	mCRPC	mCRPC	mCRPC
G3/4 adverse events (%)	Poon et al.	CHAARTED	Poon et al.	TAX 327	CUP/EAP Cabazitaxel	
					Asia	Europe
Febrile neutropenia	12.5	6.1	14.1	3.0	15.1	4.8
Neutropenia	40.6	12.1	47.4	32.0	27.3	17.1
Thrombocytopenia	0	0.3	0	1.0	1.7	1.0
Anaemia	3.1	1.3	10.6	5.0	12.2	3.1
Neuropathy	0	0.5	0	0	N/A	N/A
Fatigue	0	4.1	0	5.0	4.7	6.8
Diarrhoea	0	1.0	1.8	0	6.4	3.0
Stomatitis	0	0.5	1.8	0	N/A	N/A

1. Poon DMC, et al. *Asia-Pac J Clin Oncol*. 1-6. 2. Poon DMC, et al. *Prostate Int*. 2015;3:51-55. 3. Sweeney CJ, et al. *N Engl J Med*. 2015;373:737-46. 4. Tannock, et al, *N Engl J Med*. 2004; 351:1502-1512. 5. Malik et al. ASCO GU 2014

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Asian population: More susceptible to docetaxel's myelosuppression

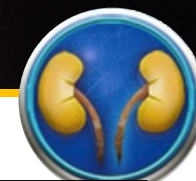


- 120 phase II/III studies (lung, breast etc) with **docetaxel monotherapy (q3wk)** as treatment arm
- Logistic regression for the higher incidence (>70%) of **grade 3 and 4 neutropenia**

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Studies conducted in Asia	2.20	0.93–5.22	0.073	19.0	3.64–99.0	<0.001
Docetaxel dose	1.01	0.99–1.03	0.266	1.08	1.03–1.13	0.001
PS >1	0.99	0.96–1.01	0.287	0.99	0.96–1.02	0.444
Median age	0.97	0.91–1.03	0.300	1.02	0.94–1.10	0.598
Percentage of female	1.01	1.00–1.02	0.082	Excluded		
Treatment line (≥2nd line)	0.50	0.24–1.02	0.057	Excluded		

OR odds ratio, CI confidence interval, PS >1 percentage of the participants whose performance status was >1

Androgen-signalling pathway inhibitors adverse events: Asian vs Global



Abiraterone

Post-chemo

Chemo-naive

G3/4 adverse events (%)	Poon et al.	COU-AA-301	Poon et al.	COU-AA-302
Hypertension	5.8	1.0	6.9	4.0
Hypokalaemia	3.8	3.8	3.4	2.0
Peripheral oedema	0	2.3	5.2	<1.0
Hepatic dysfunction	1.9	3.4	0	9.7
Discontinuation due to AEs	1.9	13	5.2	13

Enzalutamide

Post-chemo

Chemo-naive

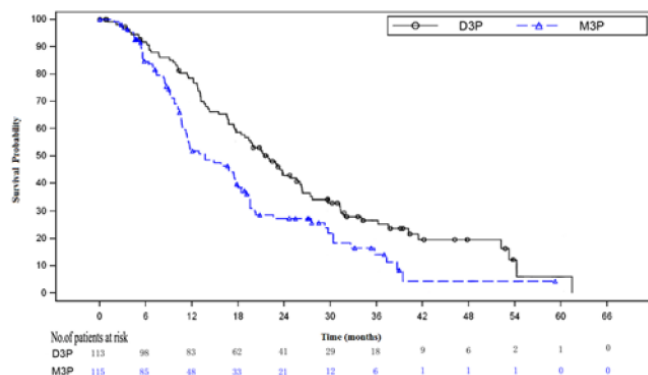
G3/4 adverse events (%)	Poon et al.	AFFIRM	Poon et al.	PREVAIL
Hypertension	7.7	4.0	11.8	7.0
Fatigue	0	6.0	5.9	2.0
Hepatic dysfunction	0	<1.0	2.9	<1.0
Discontinuation due to AEs	0	8.0	8.0	6.0

1. Poon DMC, et al. *BMC Urol.* 2016 Mar. 2. Poon DMC, et al. *Clin Genitourin Cancer.* 2018 Oct; 3. de Bono JS, et al. *N Engl J Med.* 2011 May; 4. Ryan CJ et al, *N Engl J Med.* 2013 Jan. 5. Scher HI et al. *N Engl J Med.* 2012 Sep. 6. Beer TM et al. *N Engl J Med.* 2014 Jul

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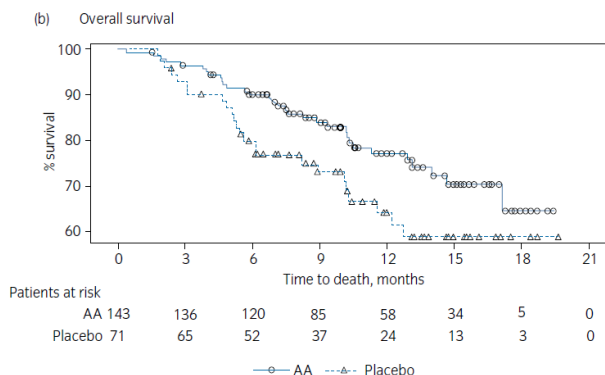
Treatment efficacy similar between Asian and Caucasian

Docetaxel Chinese



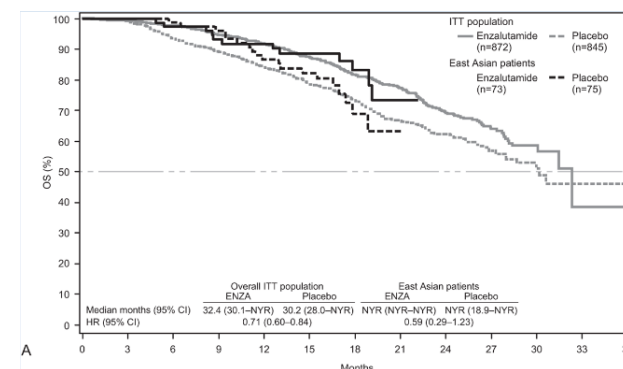
Chinese OS: **HR: 0.63**
TAX 327 OS: **HR 0.76**

Abiraterone Chinese



Chinese OS: **HR 0.60**
COU-AA-301 OS: **HR 0.65**

Enzalutamide East Asian



East Asian OS: **HR 0.59**
PREVAIL OS: **HR 0.71**

Docetaxel pharmacokinetics

Population Pharmacokinetics/Pharmacodynamics of Docetaxel in Phase II Studies in Patients With Cancer

1992-1994

582 pts (breast, NSCLC, ovarian etc) from 24 phase II open studies

Table 5. Logistic Regression Model for Febrile Neutropenia (N = 582)

Predictor	P	Odds Ratio	95% CI
CLf	.0012	3.03	1.55-5.93
AAG	.0056	0.28	0.12-0.69

NOTE. Incidence, 4.7% (26 of 582 patients).

Docetaxel clearance is sig. predictor for febrile neutropenia

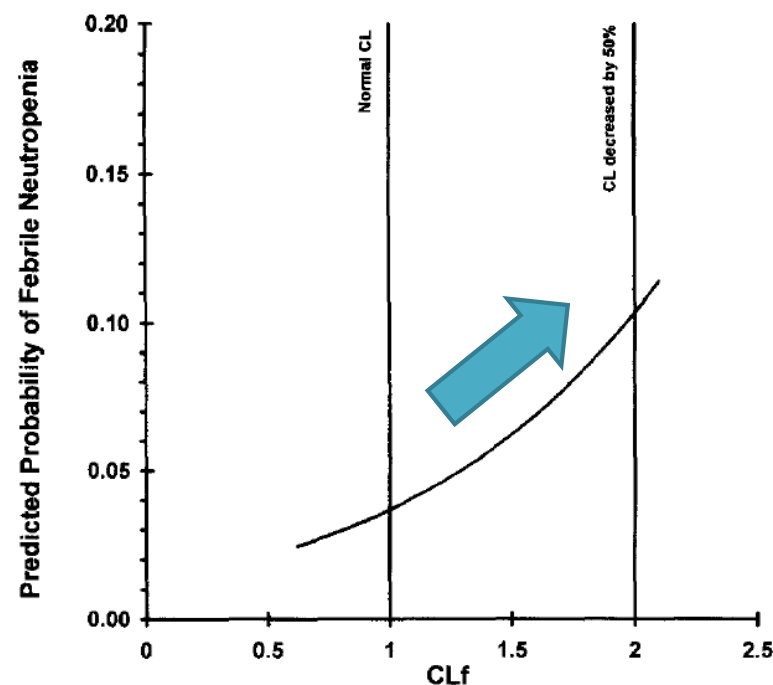
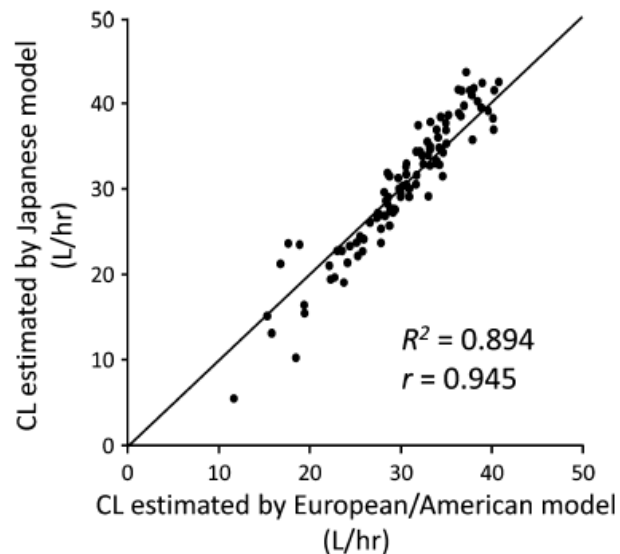


Fig 3. Model-predicted probability of febrile neutropenia as a function of CLf for a patient with median AAG. Reference vertical lines denote normal CL (CLf = 1) and 50% reduced CL (CLf = 2).

Journal of Clinical Oncology, Vol 16, No 1 (January), 1998: pp 187-196

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Japanese vs Caucasian: Docetaxel PK comparison



Similar PK between Japanese and Caucasian

Table 2. Equations predicting docetaxel clearance for European/American and Japanese populations

Authors	Equations predicting docetaxel clearance	ω CL (%)
Bruno <i>et al.</i> ⁽¹⁸⁾	$CL = BSA (22.1 - 3.55 AAG - 0.095 AGE + 0.225 ALB) (1 - 0.334 HEP)$	33
Tanigawara <i>et al.</i> ⁽¹⁹⁾	$CL = BSA (37.6 - 6.41 AAG - 0.191 AGE + 0.0436 ALB) (1 - 0.209 HEP)$	25

AAG, α 1-acid glycoprotein level (g/L); ALB, albumin level (g/L); AGE (years); BSA, body surface area (m²); CL, total body clearance (L/h); HEP, complication of hepatic dysfunction indicated by HEP = 1 (presence) or HEP = 0 (absence).

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Cancer Sci. 2015 May

Difference in body weight between Caucasian and Asian



2002 data

Mean BW (kg)	U.S. (50-59 years)	China (45-59 years)					
		Big City (>500k)	Town (200- 500k)	Rural 1 (Wealthiest)	Rural 2	Rural 3	Rural 4
Males	88.8	68.9	66.6	63.0	60.5	63.6	57.9
Females	76.9	61.1	59.4	57.5	54.8	58.1	52.3

- **Asian** : Smaller body build > Limited marrow reserve
> Higher risk of taxane-related myelo-suppression?

CDC US mean body weight, height, bmi 1960-2002 <http://www.cdc.gov/nchs/data/ad/ad347.pdf> A Survey on Nutrition and Health in Chinese Citizens. Wang Longde
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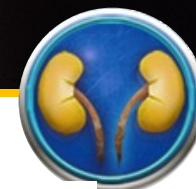
Possible solution for taxane-related haematological toxicities



- **Docetaxel Dose/schedule modification**
 - Dose modification (75mg/m^2 to 60mg/m^2)
 - Frequency alteration (q3wk to q2wk/q1wk)
- **Supportive measure**
 - Pre-emptive GCSF

Dose modification

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No sig. difference in toxicities, PSA response, & survival

2005-2008 Japanese mCRPC retrospective study

- **Standard regimen (SR)** : 60 mg/m² q4wk

- **Adapted regimen (AR)**:

1) 48 mg/m² (80 % dose) q4wk from #1

2) 60 mg/m² → toxicity → 48 mg/m² q4wk

3) 30 mg/m² q2wks x few cycles → 48 mg/m² q4wks

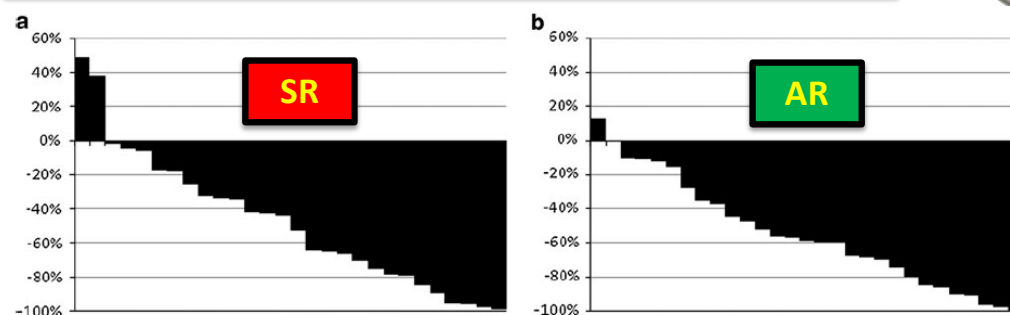
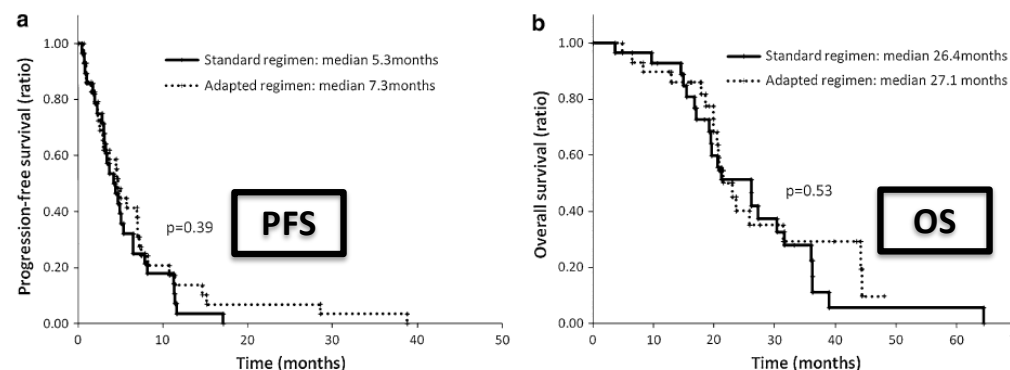


Fig. 1 Waterfall plots showing the greatest decline in prostate-specific antigen (PSA) from the baseline in patients with metastatic castration-resistant prostate cancer following docetaxel-based

chemotherapy. a Twenty-eight patients treated with the standard regimen, b 29 patients treated with adapted regimens



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Int J Clin Oncol. 2013 Aug

Docetaxel Q3wk to Q2wk schedule

2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial

75mg/m² q3wk vs 50mg/m² q2wk

Pirkko-Liisa Kellokumpu-Lehtinen, Ulrika Harmenberg, Timo Joensuu, Ray McDermott, Petteri Hervonen, Claes Ginman, Marjaana Luukka, Paul Nyandoto, Akseli Hemminki, Sten Nilsson, John McCaffrey, Raija Asola, Taina Turpeenniemi-Hujanen, Fredrik Laestadius, Tiina Tasmuth, Katinka Sandberg, Maccon Keane, Ilari Lehtinen, Tiina Luukkaala, Heikki Joensuu, for the PROSTY study group

	2-weekly docetaxel (n=170)	3-weekly docetaxel (n=176)	Hazard ratio (95% CI)	p value
Median (95% CI) TTTF (months)	5.6 (5.0–6.2)	4.9 (4.5–5.4)	1.3 (1.1–1.6)	0.014
Median (95% CI) TTP or death (months)	15.8 (13.6–18.1)	14.6 (13.2–16.0)	1.3 (1.0–1.6)	0.047
Median (95% CI) overall survival (months)	19.5 (15.9–23.1)	17.0 (15.0–19.1)	1.4 (1.1–1.8)	0.021
PSA response	84 (49%)	74 (42%)	..	0.486
Best response to treatment				0.952
Complete or partial response	39 (23%)	38 (22%)
Stable disease	78 (46%)	80 (46%)
Disease progression	14 (8%)	19 (11%)
Not available	39 (23%)	39 (22%)

Medians and 95% CIs are estimated values from Kaplan-Meier analyses. TTTF=time to treatment failure. TTP=time to progression. PSA=prostate-specific antigen.

Table 2: Summary of primary and secondary outcomes

Q2wk : better TTTF/OS

(Caveat: trial in 2004-2009, 1/5 had 2nd line Tx: insufficient subsequent treatments)

Q2wk : less toxicities

	2-weekly docetaxel (n=170)		3-weekly docetaxel (n=176)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Haematological				
Neutropenia	40 (24%)	61 (36%)	6 (3%)	93 (53%)
Leucopenia	49 (29%)	22 (13%)	36 (20%)	51 (29%)
Anaemia	144 (85%)	1 (1%)	142 (81%)	1 (1%)
Thrombocytopenia	20 (12%)	1 (1%)	20 (11%)	0
Febrile neutropenia	0	6 (4%)	0	25 (14%)
Non-haematological				
Fatigue	125 (74%)	25 (15%)	137 (78%)	26 (15%)
Myalgia	59 (35%)	4 (2%)	62 (35%)	2 (1%)
Infection without neutropenia	50 (29%)	18 (11%)	53 (30%)	21 (12%)
Infection with neutropenia	0	11 (6%)	0	43 (24%)
Diarrhoea	61 (36%)	2 (1%)	77 (44%)	4 (2%)
Nausea	58 (34%)	2 (1%)	84 (48%)	2 (1%)
Vomiting	21 (12%)	1 (1%)	20 (11%)	0
Raised alkaline phosphatase concentration	70 (41%)	16 (9%)	82 (47%)	11 (6%)
Raised AST concentration	28 (16%)	1 (1%)	33 (19%)	1 (1%)
Arthralgia	50 (29%)	1 (1%)	67 (38%)	2 (1%)
Pain	109 (64%)	11 (6%)	113 (64%)	12 (7%)
Watery eyes	86 (51%)	3 (2%)	93 (53%)	3 (2%)

We also assessed fever in the absence of neutropenia, serum bilirubin, alanine aminotransferase, or creatinine, alopecia, anorexia, allergic reactions, nail changes, dermatological adverse events, stomatitis, sensory neuropathy, motor neuropathy, bone pain, or weight loss, but no significant differences were seen between groups. AST=aspartate aminotransferase.

Table 3: Adverse events

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Lancet Oncol. 2013 Feb

Pre-emptive GCSF for Docetaxel's FN prevention



- **383** mCRPC (from Jan 2013 – Jul 2018) and mHSPC patients (from Aug 2016 – Jul 2018) in 6 HK public oncology centers that had received docetaxel

	Entire cohort (n=383)	mHSPC (n= 101)	mCRPC (n=282)	mCRPC 1 st line (n=222)	mCRPC 2 nd line or beyond (n=60)
Reduced starting dose (<75mg/m ²)	114 (29%)	10 (9%)	104 (36%)	67 (30%)	37 (61%)
Pre-emptive GCSF	72 (18%)	27 (26%)	45 (15%)	40 (18%)	5 (8%)
FN	61 (15%)	13 (12%)	48 (17%)	39 (17%)	11 (18%)
FN @ 1 st cycle	40 (10%)	9 (8%)	31 (10%)	25 (11%)	6 (10%)
G3/4 neutropenia	153 (39%)	31 (30%)	122 (43%)	92 (41%)	30 (50%)

Poon et al. Unpublished data

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Pre-emptive GCSF for Docetaxel's FN prevention



Regression analysis of febrile neutropenia at 1st cycle

variable	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Pre-emptive GCSF	0.22	0.05 - 0.96	0.04	0.21	0.05 - 0.94	0.04
Visceral met	1.79	0.84 - 3.81	0.13	1.59	0.67 - 3.91	0.31
Comorbidities	0.83	0.42 - 1.65	0.60	0.71	0.32 - 1.56	0.39
Age	0.99	0.95 - 1.04	0.78	1.00	0.95 - 1.08	0.77
BMI	0.94	0.85 - 1.03	0.17	0.91	0.8 - 1.03	0.14
BSA	1.54	0.17 - 13.62	0.70	7.21	0.43 - 120.18	0.17
Albumin	1.03	0.96 - 1.11	0.47	1.04	0.96 - 1.12	0.36
Lymphocyte	0.64	0.38 - 1.10	0.11	0.64	0.35 - 1.16	0.15
Neutrophil	1.02	0.85 - 1.24	0.80	0.98	0.79 - 1.21	0.86
Haemoglobin	0.95	0.78 - 1.15	0.57	0.99	0.75 - 1.30	0.94
ALP	1.00	1.00 - 1.00	0.29	1.00	1.00 - 1.00	0.22
PSA	1.00	1.00 - 1.00	0.70	1.00	1.00 - 1.00	0.78
ECOG level (0 - 1 vs 2 - 3)	3.33	1.38 - 8.02	0.01	3.28	1.06 - 10.15	0.04
no. of bone mets (0 - 3 vs > 3)	0.67	0.32 - 1.40	0.29	0.59	0.25 - 1.40	0.23
Starting dose	1.00	0.47 - 2.10	0.99	0.61	0.23 - 1.62	0.32
Disease status: mCRPC (1st line) vs mHSPC	0.73	0.32 - 1.70	0.47	0.88	0.32 - 2.43	0.81
Disease status: mCRPC (1st line) vs mCRPC (2nd line)	0.94	0.36 - 2.42	0.89	1.15	0.39 - 3.40	0.81

Poon et al. Unpublished data

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Hong Kong Consensus on prostate cancer management



Review

Consensus statements on the management of metastatic prostate cancer from the Hong Kong Urological Association and Hong Kong Society of Uro-Oncology

BJUI
BJU International

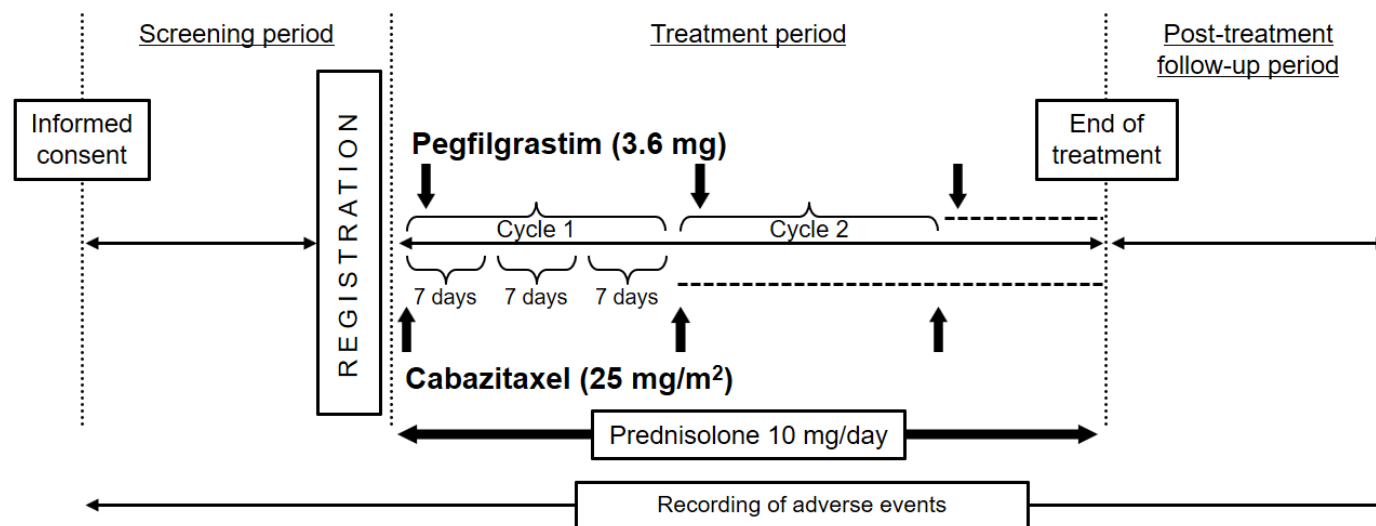
Darren Ming-Chun Poon*, Chi-Kwok Chan†, Tim-Wai Chan‡, Foon-Yiu Cheung§, Philip Wai-Kay Kwong¶, Eric Ka-Chai Lee**, Angus Kwong-Chuen Leung††, Simon Yiu-Lam Leung‡‡, Wai-Kit Ma§§, Hing-Shing So¶¶, Po-Chor Tam§§ and Lap-Yin Ho***

with high-volume disease was included in the former trial (96.9% in the Hong Kong study vs 66.2% in the CHAARTED trial) [6,29]. The risk of chemotherapy-related haematological toxicities, however, may be higher among Chinese patients, so careful patient selection and consideration of granulocyte colony-stimulating factor is necessary before starting the combination therapy [29].

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BJU Int 2018; 121: 703–715

Pre-emptive GCSF in Japanese mCRPC with Cabazitaxel



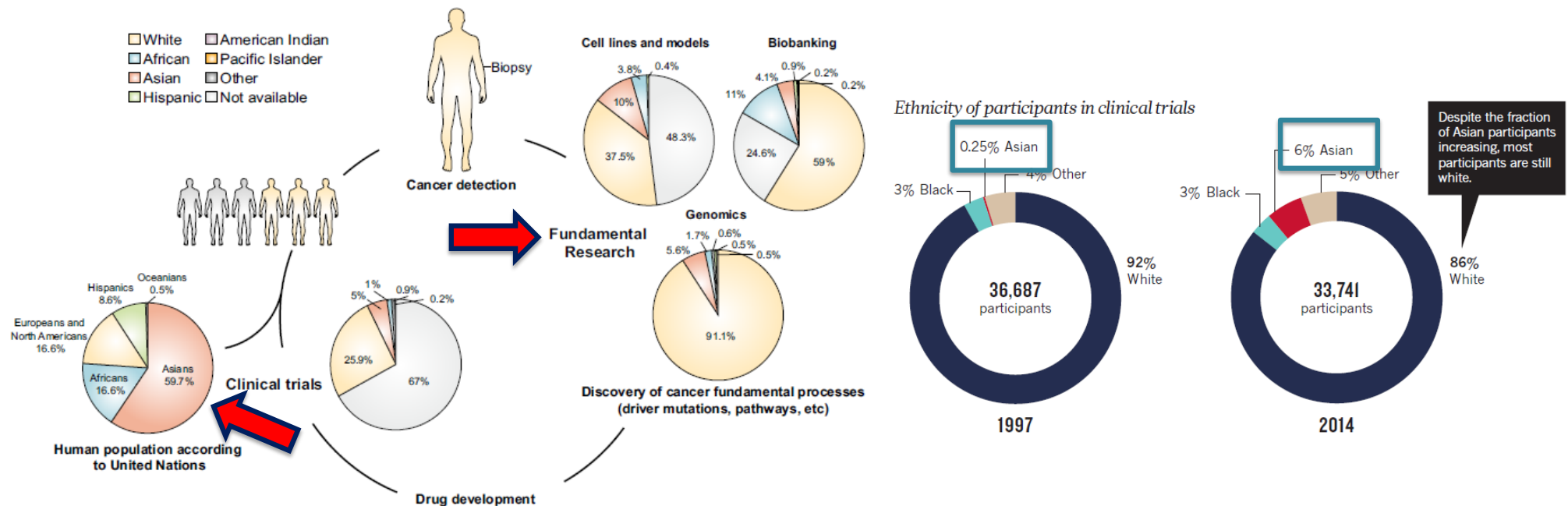
Febrile neutropenia rate

- **9%** with primary GCSF (n=21) vs
- **54%** without primary GCSF (n=44, Japanese phase I study)

Jpn J Clin Oncol. 2019 Apr; Int J Clin Oncol. 2015 Oct

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Racial and Ethnic difference in cancer research

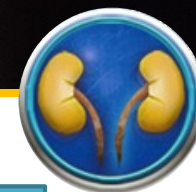


Insufficient Asian contribution in clinical trials and fundamental research

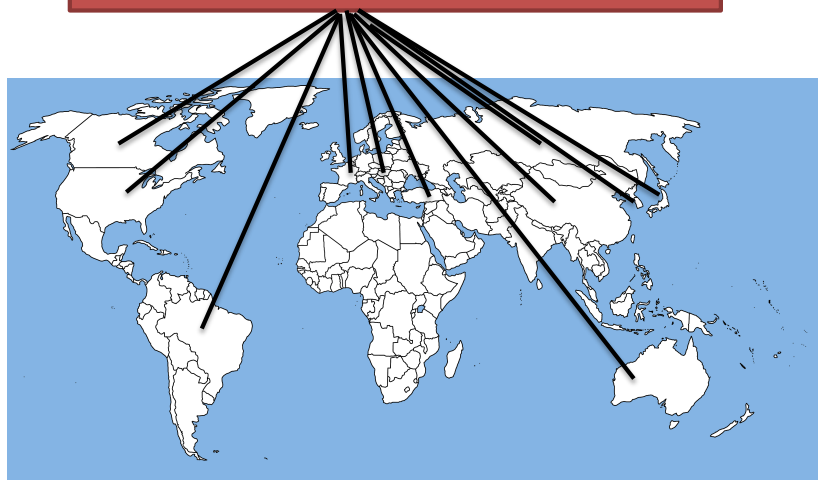
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Sci Rep. 2018 Sep; Nature. 2018 May

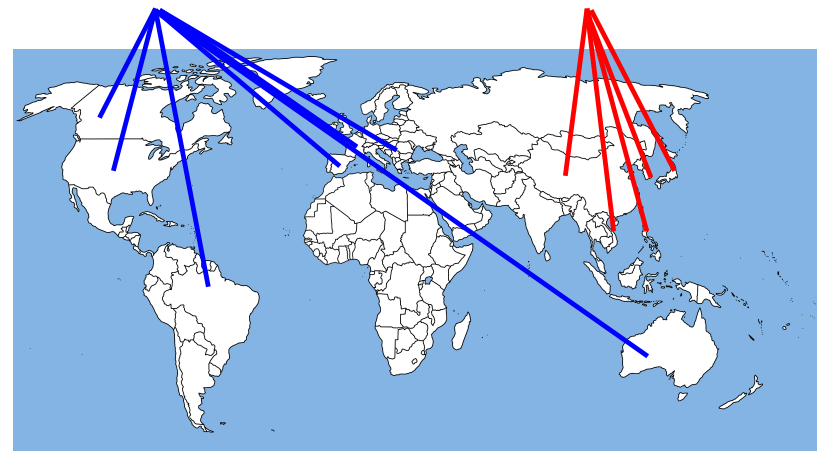
Ethnicity in drug development



Global trial involving different ethnicity



Bi-regional multicentre trial?



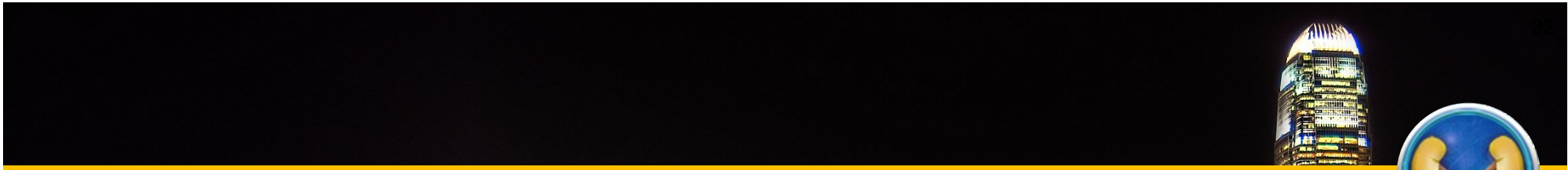
What if major ethnic differences exist in disease or pharmacology?

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Summary



- Clear **inter-ethnic difference** in pharmacology (**esp cytotoxic's toxicity**) exists
- **Asian PCa patients**
 - Higher risk of haematological complications with taxane
 - **No obvious inter-ethnic difference in PKs of docetaxel**
 - May related to **smaller body build with limited marrow reserve**
 - Well tolerate to AR agents
 - No significant difference in survival outcome to rest of the world
- To alleviate the risk of **taxane-related myelosuppression** in Asian PCa patients
 - **Dose/schedule modification**
 - pre-emptive use of **GCSF**
- **Pharmaco-ethnicity** should be taken into account in **future trials and fundamental cancer research**



My Home sweet home



Thank you for your attention!

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CUHK campus

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