Recent experiences to review data from MRCTs and progress of research on ethnic factors

Dr Yoshiaki Uyama

Pharmaceuticals & Medical Devices Agency (PMDA)

Visiting Professor, Graduate School of Advanced Clinical Science, Chiba University

Visiting Professor, Graduate School of Medicine, Nagoya University

Recent experiences to review MRCT data for regulatory approval

Product Overview

- New active ingredient indicated for the treatment of schizophrenia
- Phase 3 GCT
  - Conducted in Japan, Korea, Taiwan
  - Number of patients
    Total: N=323,
    Japan: N=156, Korea: N=71, Taiwan: N=96
  - Primary endpoint: Change of Positive and Negative Syndrome Scale (PANSS) total score from baseline

Pre-consideration about ethnic factors

- Intrinsic factors
  - There was no major discrepancy in PK data between Japanese (single and multiple dose study data) , Korean and Taiwan (other global phase 3 study data)

- Extrinsic factors
  - Common diagnostic criteria in all regions
  - Atypical antipsychotic drugs are widely used for schizophrenia in all regions
  - Training to ensure inter-rater reliability

Efficacy

Change of PANNS total score from baseline

		N	Change of PANNS total score[a]	Difference between groups [b]
All region	Placebo	164	6.9 ±19.13	-9.7[-14.0, -5.4]
	Paliperidone	159	-3.1 ±20.32	
Japan	Placebo	79	8.8 ±23.26	-11.6[-18.4, -4.8]
	Paliperidone	77	-3.0 ±19.72	
Korea	Placebo	38	5.3 ±11.93	-12.5[-20.6, -4.3]
	Paliperidone	33	-7.6 ±20.94	
Taiwan	Placebo	47	5.0 ±15.87	-4.7[-12.2, 2.7]
	Paliperidone	49	-0.1 ±20.68	

a: Mean ± SD
b: LS mean [95CI]

Safety

Main adverse events in subgroups (country)

	All region		Japan		Korea		Taiwan	
	Placebo	Paliperi-done	Placebo	Paliperi-done	Placebo	Paliperi-done	Placebo	Paliperi-done
N	164	159	79	77	38	33	41	49
Total	81.7	85.5	77.2	79.2	84.2	81.8	87.2	98.0
Insomnia	15.2	17.0	3.8	6.5	23.7	24.2	27.7	28.6
Injection site pain	6.7	13.2	5.1	6.5	5.3	24.2	10.6	16.3
Nasopharyngitis	6.1	12.6	8.9	18.2	5.3	9.1	2.1	6.1
Psychiatric symptom	26.2	11.3	39.2	18.2	23.7	3.0	6.4	6.1
Extrapyramidal disorder	4.9	10.1	2.5	7.8	5.3	9.1	8.5	14.3
Anxiety	7.9	6.3	1.3	0	23.7	18.2	6.4	8.2

%

Evaluation of the results (consistency)

- Efficacy
  - PANNS change from baseline (the primary endpoint) was similar in Japanese and Korean population, but was smaller in Taiwan population
    - possibly due to enormous exacerbation in a portion of subjects in Paliperidone group, but the responder rate to the drug was no difference among all populations
- Safety
  - Incidence rates of some adverse events such as insomnia, psychiatric symptom and anxiety differed but most of events were mild to moderate and no major difference on severity among three regions.

Review experiences of GCT data

- Ethnic factor consideration is important even in Asian GCTs
- Extrinsic ethnic factors such as concomitant therapies sometimes have impacts on data evaluation
- PPK data are useful for ethnic factor consideration
- Confirming efficacy in overall population and consistency evaluation in Japanese sub-population
  - limitation in evaluating data when sample size was small
- Differences in adverse event rate are not uncommon; partly due to difference on categorization or data collection process of adverse events in GCTs

Recent scientific advances on impacts of ethnic factors in drug responses

Ethnic differences

CBZ-induced SJS/TEN & *HLA-B*1502*

- *HLA-B*1502* screening could provide a benefit in countries, in which *HLA-B*1502* is relatively prevalent

	HLA-B*1502-positive with alternative medication (N=215)	HLA-B*1502-Negative with CBZ (N=4120)	Estimated historical incidence
CBZ-induced SJS/TEN	0% (0/0)	0% (0/0)	0.23%

Chen P et al, N Engl J Med, 364: 1126-1133, 2011
Chung WH et al, Nature, 428: 486, 2004

- However, CBZ-induced SJS/TEN patients carrying *HLA-B*1502* have not been found in Japanese

(Ozeki T et al, *Hum Mol Genet*, 2011, Kashiwagi M et al, *J Dermatol*, 2008, Kaniwa N et al, *Epilepsia*, 2008)

Biomarker for CBZ-induced SJS/TEN in Japanese

- In Japanese, association with a different allele, HLA-A*3101, has been reported

Ozeki T et al, Human Molecular Genet, 2010

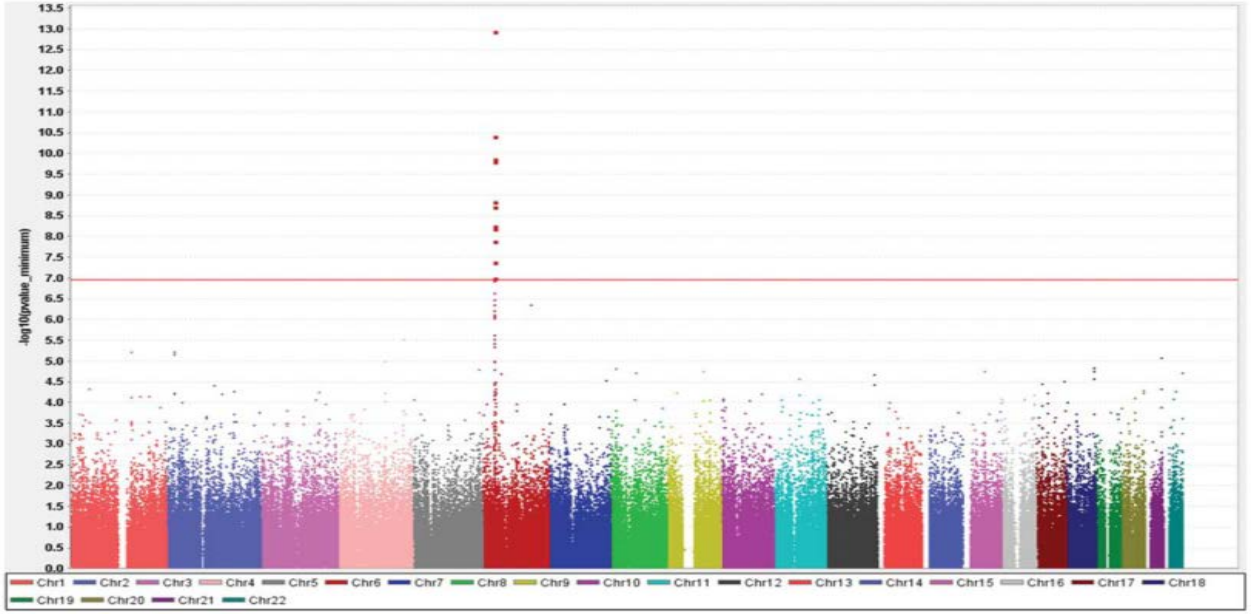


Figure 1. $-\mathrm{Log}_{10}$ *P*-value plots at the GWAS. Each dot represents *P*-value obtained from GWAS using 53 patients with carbamazepine-induced cutaneous adverse drug reactions and 882 subjects of a general population in Japanese. The *Y*-axis represents the $-\log_{10}$ of the minimal *P*-values calculated by Fisher's exact tests for three models: dominant, recessive and allele frequency models in the case–control association study.

- Interestingly, similar results were found in European population

McCormack M et al, N Engl J Med, 364: 1134-1143, 2011

CBZ Label in Japan

貯法：
錠　：室温保存
細粒：防湿、室温保存
使用期限：
包装に表示の使用期限内に使用すること
使用期限内であっても、開封後はなるべく速やかに使用すること

向精神作用性てんかん治療剤・躁状態治療剤
処方せん医薬品
（注意－医師等の処方せんにより使用すること）

テグレトール®錠100mg
テグレトール®錠200mg
テグレトール®細粒50%
Tegretol®
カルバマゼピン製剤

承認番号	錠100mg：20300AMZ00826000 錠200mg：20300AMZ00827000 細粒50%：21500AMZ00527000		
	錠100mg	錠200mg	細粒50%
薬価収載	1992年7月	1992年7月	2004年7月
販売開始	1992年7月	1966年3月	1969年3月
再評価結果	－	1975年6月	
効能追加	－	1990年3月	

NOVARTIS

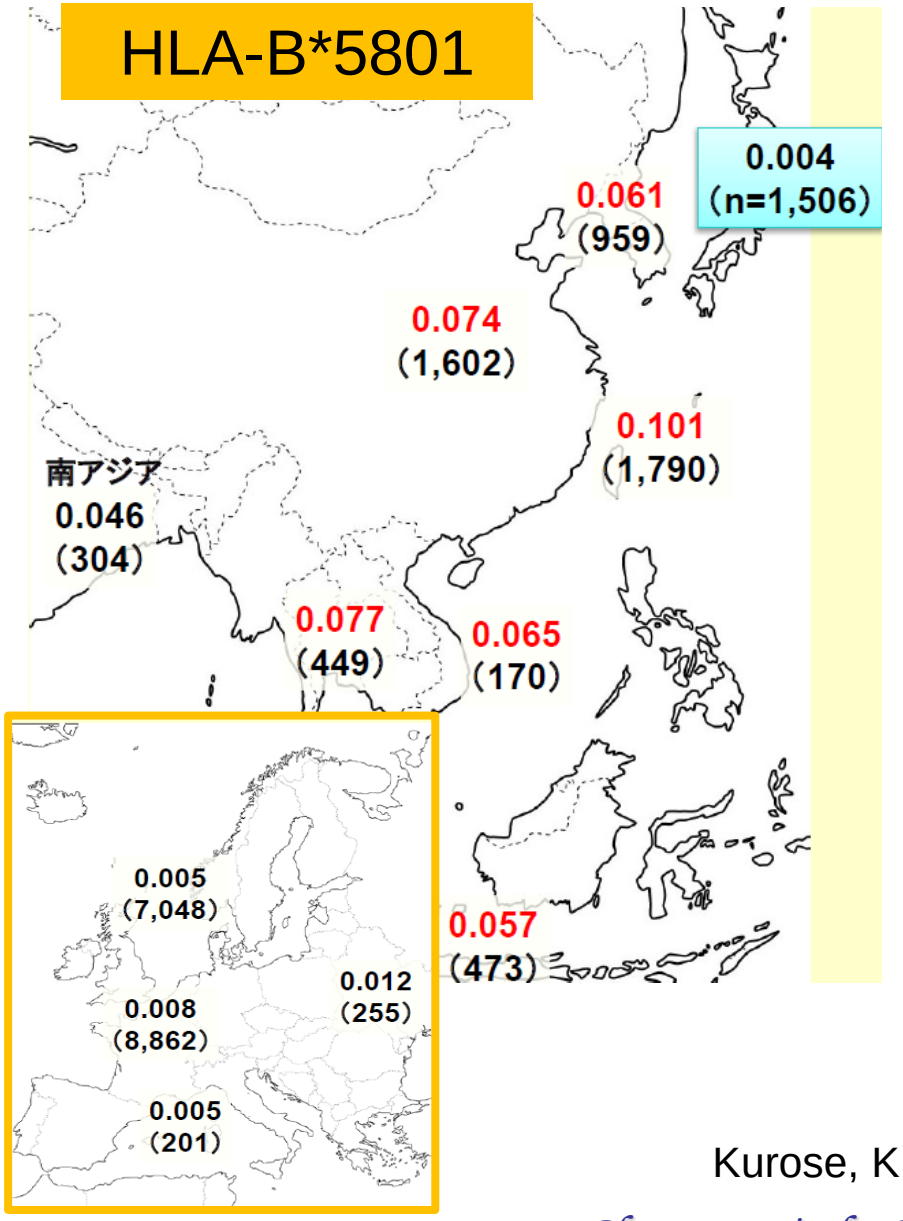
＊＊(6) 日本人を対象としたレトロスペクティブなゲノムワイド関連解析において、本剤による皮膚粘膜眼症候群、中毒性表皮壊死融解症及び過敏症症候群等の重症薬疹発症例のうち、*HLA-A*3101*保有者は58%（45/77）であり、重症薬疹を発症しなかった集団の*HLA-A*3101*保有者は13%（54/420）であったとの報告がある。[4]
漢民族（Han-Chinese）を祖先にもつ患者を対象とした研究では、本剤による皮膚粘膜眼症候群及び中毒性表皮壊死融解症発症例のうち、ほぼ全例が*HLA-B*1502*保有者であったとの報告がある。[5,6] 一方、日本人を対象とした研究において本剤による重症薬疹発症例と*HLA-B*1502*保有との明らかな関連性は示唆されていない。[4]
なお、*HLA-B*1502*アレルの頻度は漢民族では0.019-0.124、日本人では0.001との報告がある。[7]

- Results of Genome-Wide Association Study (GWAS) in Japanese population
  - CBZ-induced SJS/TEN associated with HLA-A*3101
- The association with HLA-B*1502 is revealed in Han-Chinese, but not in Japanese

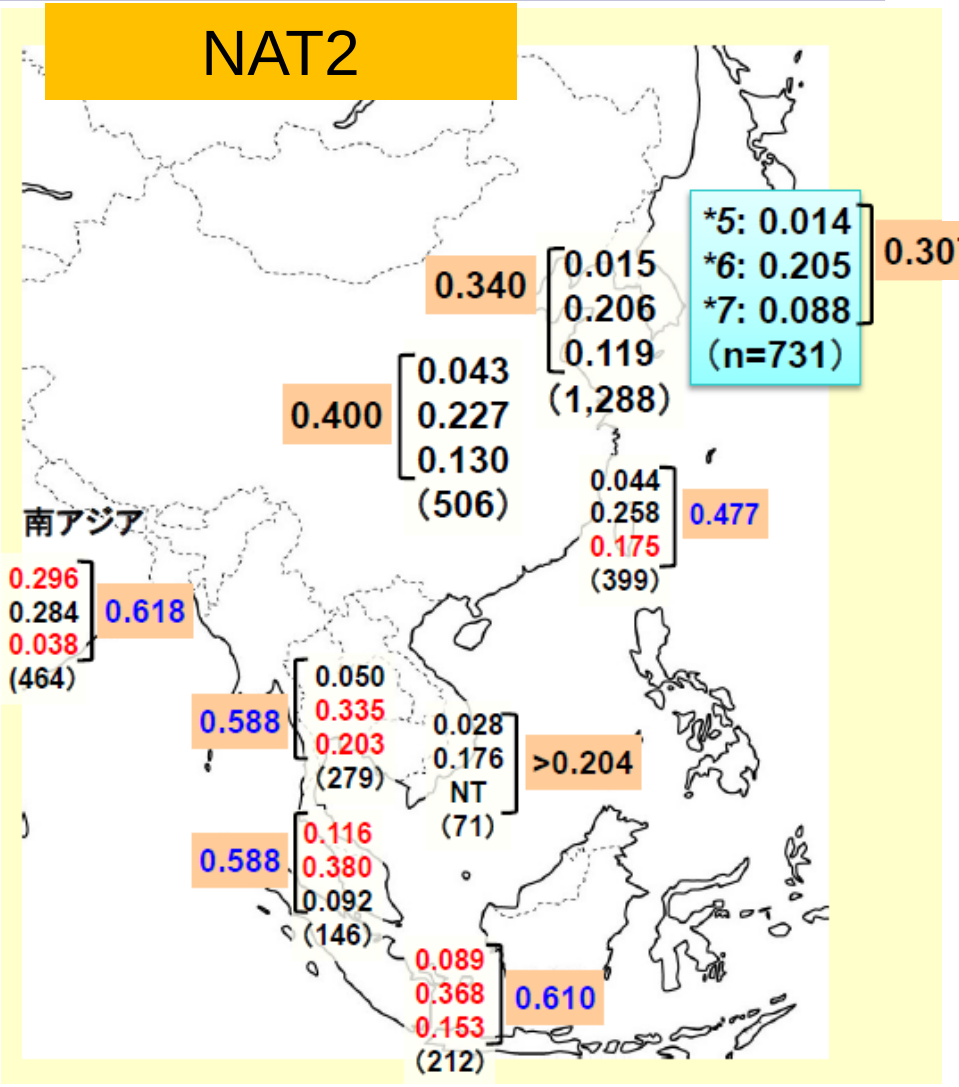
Clinical meaningfulness of HLA-A*3101 on patient selections is still unknown

Genetic differences among Asian populations

HLA-B*5801



NAT2



Kurose, K. et al., *Drug Metab Pharmacokinet* **27**, 9-54 (2012).

Contribution of OATP1B1 on PK difference of HMG-CoA reductase inhibitor

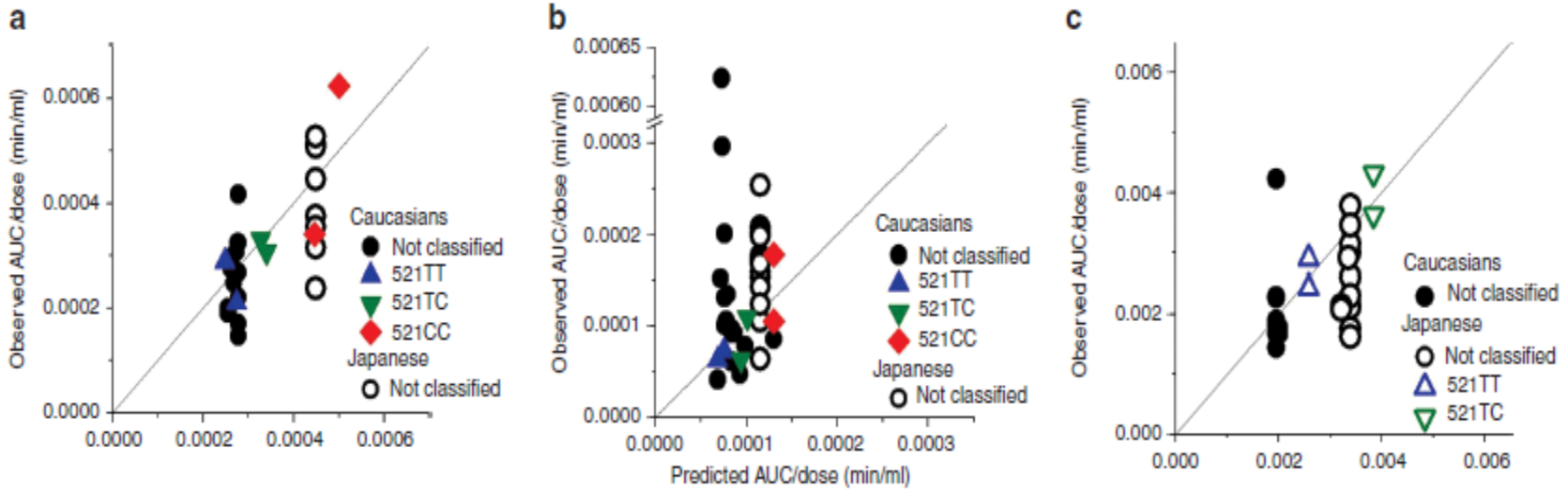


Figure 6 Comparisons of observed and predicted dose-normalized area under the concentration–time curve (AUCs) of (a) rosuvastatin, (b) atorvastatin, and (c) pitavastatin, after considering BW, genotype, and the ratio of the OATP1B1-mediated intrinsic transport activity in Japanese subjects to that in Caucasian subjects

Tomita, Y. et al, *Clin Pharmacol Ther* **94**, 37-51 (2013)

Ethnic Similarities

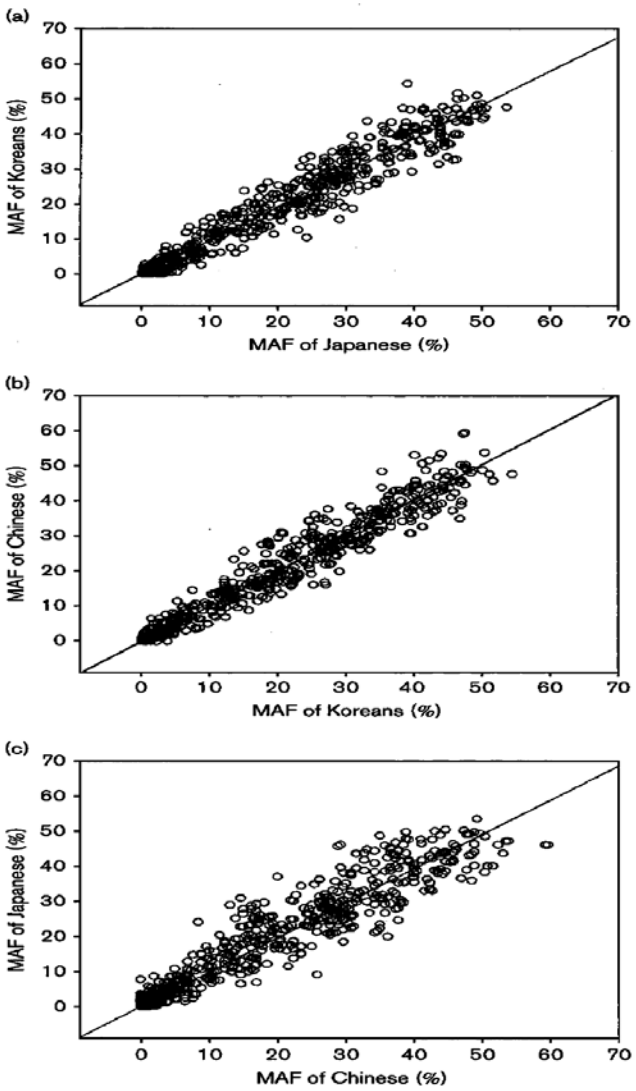
Ethnic similarities on UGT

Supplementary Table 2. The Comparison of Core Marker Minor Allele Frequencies between Koreans and Other Ethnic Groups

Gene	SNP	KR vs. CH		KR vs. JP		KR vs. AA		KR vs. EA	
		P	$P^{cor.}$	P	$P^{cor.}$	P	$P^{cor.}$	P	$P^{cor.}$
UGT1A1	*rs4124874G>T*	0.074	NS	0.808	NS	1.05E-10*	2.52E-09*	0.050*	NS
	rs10929302G>A	0.294	NS	0.294	NS	1.13E-05*	2.71E-04*	0.0151*	NS
	rs4148323G>A (R71G)	0.318	NS	0.309	NS	3.01E-06*	7.22E-05*	3.01E-06*	7.22E-05*
UGT2B7	*rs12233719G>T* (A71S)	0.056	NS	0.030	NS	2.39E-05*	5.74E-04*	3.42E-05*	8.21E-04*
	rs7439366C>T (H268Y)	0.076	NS	0.188	NS	4.36E-11*	1.05E-09*	0.002*	0.048*
UGT2B15	*rs1902023G>T* (D85Y)	0.002*	0.048*	0.377	NS	0.01*	NS	0.006*	NS

KR, Korean; CH, Chinese; JP, Japanese; AA, African American; EA, European American.
Values indicate the *p* value of difference between the two ethnic groups calculated by Fisher's exact test.
*Values indicate numbers below 0.05. *p* values were adjusted for the multiple testing by applying Bonferroni correction (n=24, which is a number of total tests in the table).

Kim, J.Y. *et al. Yonsei medical journal* **55**, 232-9 (2014).



Correlation of minor allele frequencies between population

- The frequencies of 1936 variants representing 225 genes encoding drug-metabolizing enzymes and transporters were determined from 786 healthy participants (448 Korean, 208 Japanese, and 130 Chinese)
- No major ethnic differences among Chinese, Korean and Japanese populations

Yi, S. et al. Pharmacogenetics and Genomics 24, 477-85 (2014).

Other related update

Ethnicities Evaluation in NDAs of US

Table 3. Reported Race and Ethnicity of US Participants Within Food and Drug Administration-Approved Oncology New Molecular Entities

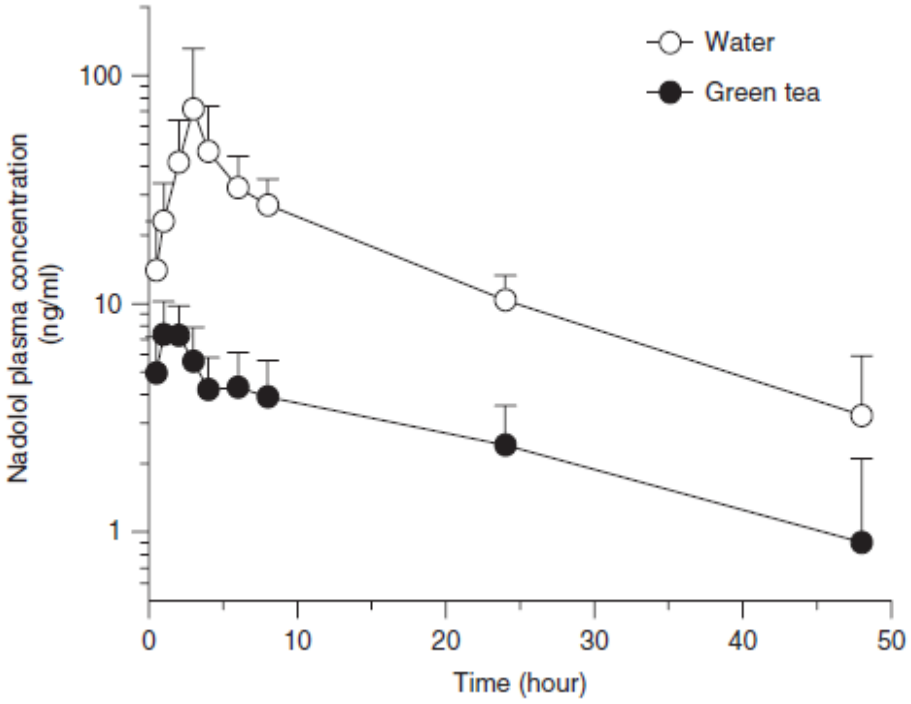
Race/Ethnicity	NME 1	NME 2	NME 3	NME 4	NME5	NME 6	NME 7	NME 8	NME 9	NME 10
White	93.33%	89.86%	80.56%	72.97%	75.00%	81.53%	84.04%	81.78%	58.70%	86.81%
Black/African American	3.64%	7.25%	9.26%	27.03%	10.29%	12.74%	7.45%	10.17%	26.81%	7.69%
Hispanic/Latino	2.42%	0%	6.48%	0%	8.82%	0%	0%	5.08%	13.04%	2.20%
Asian	0%	1.45%	2.78%	0%	4.41%	2.55%	2.13%	2.54%	0.72%	2.20%
Other	0.60%	0%	0.93%	0%	1.47%	3.18%	0%	0%	0%	1.10%
Native Hawaiian/ Pacific Islander	0%	0%	0%	0%	0%	0%	5.32%	0%	0%	0%
American Indian/ Alaska Native	0%	0%	0%	0%	0%	0%	1.06%	0%	0.72%	0%
Not described	0%	1.45%	0%	0%	0%	0%	0%	0.42%	0%	0%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

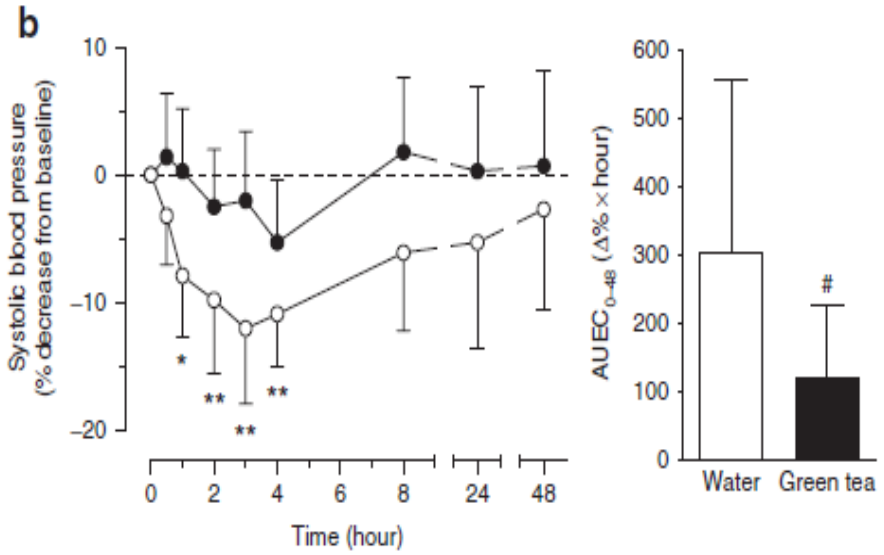
Table 4. Reported Race and Ethnicity of US Participants in 15 Pivotal Trials for Food and Drug Administration-Approved Oncology New Molecular Entities by Year

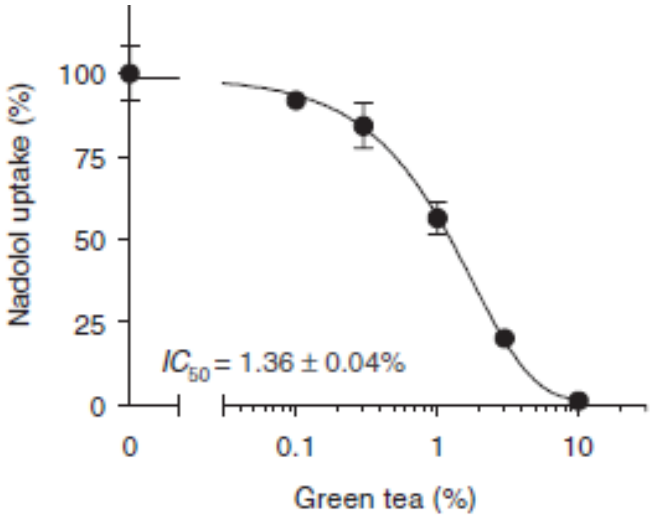
	Participants, %		
Race/Ethnicity	**2006**	**2007**	**2008**
White	87	81.26	69.87
Black or African American	8.18	10.45	19.21
Hispanic or Latino	2.90	3.24	8.73
Asian	1.06	2.70	1.31
Native Hawaiian or Pacific Islander	0.0	0.90	0.0
American Indian or Alaska Native	0.0	0.18	0.44
Other	0.53	1.08	0.44
Not Described	0.26	0.18	0.0
Total	100	100	100

Merenda, C. J NATIONAL MED ASSOC 104, 430-5 (2012).

Effects of Green Tea on Nadolol responses







Misaka, S. et al. Clin Pharmacol Ther 95, 432-8 (2014).

Challenges for better MRCTs which are acceptable by multiple agencies

More scientific evidences have been reported;

- facilitate our understanding about ethnic factors in drug responses
  - Co-promotion of regulatory science research on ethnic factors for expanding our scientific knowledge about its impacts on drug efficacy/safety in both populations
    - Accumulation of scientific knowledge on ethnic similarities/differences
  - Information exchange regarding review experiences/guideline on data from MRCTs
    - Common points to consider in reviewing data from MRCTs