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Impact of CYP2C93, CYP2A64, and ABCG2 Variants on Osimertinib-Related Toxicity and Treatment Failure in a Thai NSCLC Cohort

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ABSTRACT

Compared with earlier epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), osimertinib delivers superior therapeutic activity and produces fewer grade 3 or higher adverse drug reactions (ADRs) in individuals with advanced non-small cell lung cancer (NSCLC) carrying epidermal growth factor receptor (EGFR) mutations. Nonetheless, treatment responses to this agent have been shown to differ among ethnic groups. For this reason, additional investigation is required to determine how single-nucleotide polymorphisms (SNPs) within cytochrome P450 (CYP450) enzymes and transporter genes may influence therapeutic outcomes and ADR profiles among Thai recipients of osimertinib, with the aim of improving individualized cancer therapy. In this observational cohort incorporating retrospective and prospective data, 63 Thai NSCLC patients were treated with osimertinib monotherapy at a daily dose of 80 mg. Each subject was genotyped for seventeen SNPs within genes implicated in metabolism or transport of the drug. Chi-square and Fisher's exact tests were applied to examine associations between genetic variants and clinical endpoints such as ADR occurrence and objective response rate (ORR). Additionally, Kaplan–Meier curves with log-rank analyses were used to explore links between genotype and median time to treatment failure (TTF) or progression-free survival (PFS).

Six genetic markers—rs2231142 and rs2622604 in ABCG2, rs762551 in CYP1A2, rs1057910 in CYP2C9, rs28371759 in CYP3A4, and the CYP2A6 deletion allele (CYP2A64)—were found to significantly elevate ADR frequency. Two variants, rs2069514 in CYP1A2 and rs1057910 in CYP2C9, were connected with shorter median TTF, while rs28399433 in CYP2A6 and rs1057910 in CYP2C9 were associated with reduced median PFS. Notably, rs1057910 in CYP2C9 had simultaneous effects on ADR risk, TTF, and PFS. Furthermore, carriers of the CYP2A6 heterozygous non-4/*4 genotype demonstrated a markedly increased incidence of ADRs and exhibited a 27.0% rate of dose reduction. The study identified several SNPs that correlate with heightened ADR occurrence as well as diminished PFS and TTF in Thai NSCLC patients receiving osimertinib. The allele distributions of CYP2C9 (*3) and CYP2A6 (*4) differed from those seen in other populations and were linked to elevated ADR rates. These data emphasize the relevance of pharmacogenetic variability in NSCLC management and may support more personalized therapeutic strategies. Additionally, the incidence of ADRs and the frequency of dose modification exceeded those described in major trials such as FLAURA, AURA2, and AURA3, potentially reflecting genetic distinctions among populations.

Keywords: Non-small cell lung cancer, Pharmacogenomics, SNPs, Osimertinib, Metabolic enzymes, Transporter proteins

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Introduction

Lung cancer remains the world's most lethal malignancy, contributing to roughly 18% of cancer-related deaths [1]. Between 80% and 85% of cases fall under the category of non-small cell lung cancer (NSCLC) [2]. Among Thai individuals with NSCLC, epidermal growth factor receptor (EGFR) variants are detected frequently, appearing in 68% of cases [3]. These activating mutations are known predictors of therapeutic benefit with first- and second-generation EGFR tyrosine kinase inhibitors (TKIs), though most patients acquire resistance within 9–

12 months of therapy [4]. A principal resistance mechanism corresponds to the T790M substitution on exon 20, occurring in 50%–60% of resistant tumors, which increases ATP affinity in the receptor's kinase region and reduces susceptibility to earlier EGFR-TKIs [5].

Osimertinib is a later-generation EGFR-TKI designed to bind irreversibly to cysteine-797 in the ATP-binding pocket [6]. It effectively suppresses EGFR signaling in models with exon 19 deletions or the exon 21 L858R alteration, presenting IC50 values between 13 and 54 nmol/L. In systems possessing the T790M variant, its inhibitory strength is considerable, with IC50 values under 15 nmol/L. The compound also selectively targets mutated receptors over the wild-type form (IC50 480–1865 nmol/L) [7], which contributes to a more favorable gastrointestinal and dermatologic toxicity profile. Furthermore, osimertinib has been shown to improve overall survival in previously untreated, advanced NSCLC cases harboring EGFR mutations [8]. Metabolic clearance of the drug primarily involves CYP3A4 (44.4%), CYP2A6 (15.5%), CYP2C9 (12.0%), CYP3A5 (9.6%), and CYP2E1 (3.0%) [9]. Two major circulating metabolites—AZ5104 and AZ7550—together represent about 10% of parent exposure [10]. AZ7550 displays activity similar to the parent compound, whereas AZ5104 is roughly eight times more potent against EGFR-mutated targets [11].

A prior investigation documented that the steady-state AUCs of AZ5104 differed across populations, showing a 10%–23% lower exposure in Asians compared with Caucasians, although the mechanism for this disparity has not yet been clarified [12]. Osimertinib undergoes extensive CYP450-mediated metabolism and is transported by proteins encoded by ABCB1 (P-gp) and ABCG2 (BCRP) [10]. Because these systems are influenced by genetic variation, plasma concentrations of the drug can vary markedly among individuals. Earlier work also demonstrated that higher osimertinib levels were associated with an elevated probability of ADRs—particularly diarrhea, rash, and QTc-interval prolongation [12]. Reports from Asian cohorts further noted slightly greater QTc-prolongation rates than what was described in the FLAURA trial [13, 14]. Additional evidence linked AUC0–24, ABCB1 rs1128503, and ABCG2 rs2231137 with grade ≥2 toxicities [15]. Other EGFR-TKI studies associated CYP1A2 rs762551 with erlotinib-induced skin reactions and identified ABCB1 rs2470890 and CYP3A5 rs776746 as markers for drug-related diarrhea [16]. ABCB1 rs2032582 has been implicated in afatinib-related diarrhea [17], while impaired CYP2D6 function heightens the risk of gefitinib-associated rash [18]. Despite these findings, the relevance of CYP450 and transporter polymorphisms to osimertinib treatment outcomes remains poorly defined. Therefore, we analyzed 17 SNPs in CYP enzymes and efflux transporters that could modify the drug's pharmacokinetic and pharmacodynamic behavior to support individualized treatment strategies.

Materials and Methods

Patients and study design

This retrospective–prospective cohort consisted of 63 NSCLC patients treated between June 2022 and January 2023 at the Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. Participants had histologically verified EGFR-mutated disease, were prescribed 80 mg osimertinib once daily, were older than 18 years, and had acceptable baseline laboratory values (complete blood count, renal tests, and liver tests). Individuals taking agents known to influence osimertinib disposition or listed as toxicologically relevant in the official product monograph—itraconazole, rifampicin, simvastatin, or amiodarone [10]—were excluded. Written informed consent was obtained from all participants, and study approval was granted by the Ramathibodi Ethics Committee (COA. MURA 2022/370).

Genotyping methods

Genomic DNA was purified from 6 mL of EDTA-anticoagulated blood using a MagNaPure automated extraction system (Roche, Mannheim, Germany). Concentrations were close to 5 ng/μL, with A260/A280 values falling within 1.70–2.10. The genotyping panel included 17 SNPs: ABCB1 rs1128503; ABCG2 rs1871744, rs2231142, rs2231164, rs2622604, rs4148157; CYP1A2 rs1871744, rs2069514, rs762551; CYP2A6 *4 and rs28399433; CYP2C9 rs1057910 and rs1799853; CYP3A4 rs28371759; CYP3A5 rs10264272 and rs776746; and POR rs1057868. Real-time PCR was performed on a ViiA7 system (ABI, Foster City, CA, USA) following manufacturer guidelines. Each 96-well run contained both positive and negative controls. All loci were genotyped using TaqMan chemistry (ABI, Foster City, CA, USA).

Clinical endpoint assessment

Clinical associations between genetic variants and outcomes were evaluated for ADR frequency, median time to treatment failure (TTF), median progression-free survival (PFS), and objective response rate (ORR). Treating physicians routinely assessed ADRs using the National Cancer Institute's CTCAE version 5.0, and causality was determined with the Naranjo algorithm. TTF represented the interval from the start of osimertinib therapy until another systemic or local therapy was initiated. PFS was calculated from treatment initiation until radiographic progression or death from any cause. ORR corresponded to the proportion of patients achieving complete or partial tumor reduction according to RECIST version 1.1, as evaluated by each patient's physician.

Statistical analysis

Links between individual SNP variants and clinical endpoints—ADR occurrence, ORR, and associations with baseline characteristics—were examined using whichever test was statistically suitable: chi-square or Fisher's exact. Compliance of each polymorphism with Hardy-Weinberg Equilibrium (HWE) was checked using Fisher's exact test. Patterns of linkage disequilibrium were interrogated with Haploview 4.0. Logistic regression was conducted in two stages: an initial univariate screen followed by multivariate modeling. All variables and SNPs with $p < 0.1$ from the univariate stage were included in the multivariate analysis. Kaplan–Meier curves, along with the log-rank method, were used to compare TTF and PFS among genotype groups. All computations were executed in SPSS (Windows, version 23), and statistical significance was defined as $p < 0.05$.

The cohort size justification was derived from a longitudinal prospective study of 53 osimertinib-treated advanced NSCLC patients, which identified a meaningful association between ABCG2 rs2231137 and grade ≥2 toxicities ($p = 0.008$). Among G/G (wild-type) individuals, 22 (68.75%) developed grade ≥2 adverse events, whereas all three A/A (mutant) subjects (100%) experienced grade ≥2 toxicity [15]. Using the n4Studies calculator for binary-outcome cohort designs [19], a minimum of 58 participants was required.

Results and Discussion

Patient characteristics

Table 1 summarizes baseline demographics. The final dataset included 63 participants: 20 males (31.75%) and 43 females (68.25%). The median patient age was 68 years (range: 60–73). EGFR alterations consisted of exon 19 deletions in 42 subjects (66.7%), L858R substitutions in 19 (30.2%), a single exon 20 insertion (1.6%), and one exon 18 G719X case (1.6%). The T790M mutation appeared in 46 patients (73%). None of the recorded patient features showed statistical links with ADRs, TTF, PFS, or ORR.

Osimertinib was administered as first-line therapy in 10 cases (15.9%), second-line in 36 (57.1%), and third-line or later in 17 (27.0%). Prior systemic regimens consisted of erlotinib (40.8%), gefitinib (35.5%), platinum-doublet chemotherapy (21.9%), and mobocertinib (1.8%). Neither treatment line nor previous therapies influenced outcomes ($p > 0.05$). All individuals received 80 mg osimertinib daily. At data cutoff, the average follow-up duration was 18 months (range 10–30), and 46 participants (73%) continued treatment without dose modification. Baseline hematologic, hepatic, and renal parameters were within normal limits for all subjects.

Table 1. Baseline characteristics of patients.

Patient characteristic	Overall format: median [25th–75th percentile] or n (%)	1st-line osimertinib (n = 10)	2nd-line osimertinib (n = 36)	≥3rd-line osimertinib (n = 17)
Sex				
Female		8 (80.0%)	22 (61.1%)	13 (76.5%)
Male		2 (20.0%)	14 (38.9%)	4 (23.5%)
Age (years)		63.5 [56.0–71.5]	70.5 [61.0–73.0]	66.0 [60.0–72.0]
Body mass index (kg/m²)		22.5 [21.2–25.2]	20.8 [19.3–23.8]	21.73 [19.5–23.8]
ECOG performance status				
0		6 (60.0%)	10 (27.8%)	6 (35.3%)
1		4 (40.0%)	16 (44.4%)	10 (58.8%)
2		0 (0%)	9 (25.0%)	1 (5.9%)
3		0 (0%)	1 (2.8%)	0 (0%)

Smoking status			
Never smoker	9 (90.0%)	28 (77.8%)	14 (82.3%)
Former smoker	1 (10.0%)	6 (16.7%)	1 (5.9%)
Current smoker	0 (0%)	0 (0%)	1 (5.9%)
Passive smoker	0 (0%)	2 (5.5%)	1 (5.9%)
Stage at osimertinib initiation			
IIIA	0 (0%)	1 (2.8%)	0 (0%)
IV	10 (100.0%)	35 (97.2%)	17 (100%)
Brain metastasis at baseline	2 (20.0%)	4 (11.1%)	7 (41.2%)
EGFR mutation type			
Exon 18 G719X	0 (0%)	1 (2.8%)	0 (0%)
Exon 19 deletion	6 (60.0%)	22 (61.1%)	14 (82.4%)
Exon 20 insertion	0 (0%)	1 (2.8%)	0 (0%)
Exon 21 L858R	4 (40.0%)	12 (33.3%)	3 (17.6%)
Exon 20 T790M (acquired resistance mutation)	1 (10.0%)[a]	29 (80.6%)[b]	16 (94.1%)[b]
Dose modification			
Temporary dose interruption	1 (10.0%)	3 (8.3%)	3 (17.6%)
Permanent dose reduction	3 (30.0%)	9 (25.0%)	5 (29.4%)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.
aDe novo EGFR exon 20 T790M mutation.
bAcquired EGFR exon 20 T790M mutation.

Genotype frequencies

Genotyping was successfully obtained for every one of the 63 participants **(Table 2)**. None of the SNP distributions demonstrated any departure from Hardy–Weinberg expectations.

Table 2. Genotype and allele frequencies of the analyzed SNPs compared with reference data (PharmGKB, 2021).

SNP Identifier	Gene	Genotype	n (count)	Observed frequency (%)	Allele	Allele frequency in this study (%)	Allele frequency in previous report (%)	HWE p-value
rs1128503	ABCB1	G/G	9	14.3	G	37.3	38.9	0.69
		G/A	29	46.0	A	62.7	61.1	
		A/A	25	39.7				
rs2231142	ABCG2	C/C	31	49.2	C	70.6	70.9	0.99
		C/A	27	42.9	A	29.4	29.1	
		A/A	5	7.9				
rs2231164	ABCG2	T/T	18	28.6	T	52.4	50.4	0.75
		T/C	30	47.6	C	47.6	49.6	
		C/C	15	23.8				
rs2622604	ABCG2	C/C	38	60.3	C	76.2	81.4	0.18
		C/T	20	31.7	T	23.8	18.6	
		T/T	5	7.9				
rs4148157	ABCG2	G/G	38	60.3	G	77.8	75.0	0.49
		G/A	22	34.9	A	22.2	25.0	
		A/A	3	4.8				
rs1871744	ABCG2	T/T	27	42.9	T	65.9	72.5	0.15
		T/C	29	46.0	C	34.1	27.5	
		C/C	7	11.1				
rs2069514	CYP1A2	G/G	31	49.2	G	70.6	73.0	0.65
		G/A	27	42.9	A	29.4	27.0	
		A/A	5	7.9				

rs762551	CYP1A2	C/C	3	4.8	C	31.0	35.4	0.36
		C/A	33	52.4	A	69.0	64.6	
		A/A	27	42.9				

SNPs associated with osimertinib-related ADRs

The relationships between polymorphisms and the occurrence of ADRs are outlined in **Table 3**. A strong association was noted for CYP2C9 rs1057910, which corresponded with a higher likelihood of grade 3 adverse reactions (p = 0.003). Several variants also showed associations with specific toxicities: ABCG2 rs2622604 T/T and CYP2A6 non*4/*4 genotypes were related to diarrhea (p = 0.011 and p = 0.046). Additional links included ABCG2 rs2231142 A/A with myalgia (p = 0.007), CYP2C9 rs1057910 C/C with grade 3 acneiform rash (p = 0.012), CYP3A4 rs28371759 A/G with QTc prolongation (p = 0.001), and CYP1A2 rs762551 C/C with bullous dermatitis (p = 0.006). Full details appear in **Table 4**.

Table 3. Genotype and allele frequencies of SNPs compared with PharmGKB (2021) (continued).

SNP Identifier	Gene	Genotype	n (count)	Frequency (%)	Allele	Allele frequency in this study (%)	Allele frequency in previous report (%)	HWE p-value
CYP2A6*4	CYP2A6	non*4/non*4	54	85.7	non*4	92.9	95.3	0.28
		non*4/*4	9	14.3	*4	7.1	4.7	
		*4/*4	0	0				
rs28399433	CYP2A6	A/A	43	68.3	A	81.7	86.4	0.19
		A/C	17	27.0	C	18.3	13.6	
		C/C	3	4.8				
rs1799853	CYP2C9	C/C	63	100	C	100	99.8	0.95
		C/T	0	0	T	0	0.2	
		T/T	0	0				
rs1057910	CYP2C9	A/A	57	90.5	A	94.4	95.6	0.44
		A/C	5	7.9	C	5.6	4.4	
		C/C	1	1.6				
rs28371759	CYP3A4	A/A	60	95.2	A	97.6	98.5	0.17
		A/G	3	4.8	G	2.4	1.5	
		G/G	0	0				
rs776746	CYP3A5	A/A	5	7.9	A	32.5	27.8	0.27
		A/G	31	49.2	G	67.5	72.2	
		G/G	27	42.9				
rs10264272	CYP3A5	G/G	63	100	G	100	100	1.00
		G/A	0	0	A	0	0	
		A/A	0	0				
rs41303343	CYP3A5	−/−	63	100	no-insT	100	100	1.00
		−/T	0	0	insT	0	0	
		T/T	0	0				
rs1057868	POR	C/C	26	41.3	C	65.1	59.9	0.29
		C/T	30	47.6	T	34.9	40.1	
		T/T	7	11.1				

HWE, Hardy–Weinberg equilibrium; insT, thymine insertion.

Table 4. Summary of significant links between SNP variants and the occurrence of individual ADR types.

SNP Identifier	Gene	Genotype	ADR incidence [n/N (%)]	Type of ADR	p-value
rs2231142	ABCG2	C/C	0/31 (0)	Myalgia	0.007[a]

		C/A	0/27 (0)		
		A/A	1/5 (20.0)		
rs2622604	ABCG2	C/C	7/38 (18.4)	Diarrhea	0.011[a]
		C/T	6/20 (30.0)		
		T/T	4/5 (80.0)		
rs762551	CYP1A2	C/C	1/3 (33.3)	Bullous dermatitis	0.006[a]
		C/A	0/33 (0)		
		A/A	0/27 (0)		
CYP2A6*4	CYP2A6	non*4/non*4	12/54 (22.2)	Diarrhea	0.046[a]
		non*4/*4	5/9 (55.6)		
rs1057910	CYP2C9	A/A	0/57 (0)	Acneiform rash grade 3	0.012[a]
		A/C	0/5 (0)		
		C/C	1/1 (100)		
rs28371759	CYP3A4	A/A	11/60 (18.3)	QTc prolongation	0.001[a]
		A/G	3/3 (100.0)		

n = count of ADRs within a genotype group; N = total genotype count; (%) = event rate.
a Indicates statistical significance.

SNPs associated with osimertinib efficacy outcomes

Following the start of osimertinib therapy, 31 individuals (49.2%) achieved an objective response: one case (1.6%) met criteria for complete response, while 30 cases (47.6%) showed partial response. The remaining 32 patients (50.8%) were categorized as non-responders, consisting of 30 with stable disease (47.6%) and two with progressive disease (3.2%).

The median TTF was 19 months (range 10.3–29.0). Two polymorphisms—CYP1A2 rs2069514 in the A/A genotype and CYP2C9 rs1057910 in the A/C genotype—were significantly correlated with shorter TTF, with p-values <0.001 and 0.041, respectively. These outcomes are summarized in **Table 5** and depicted in **Figure 1**.

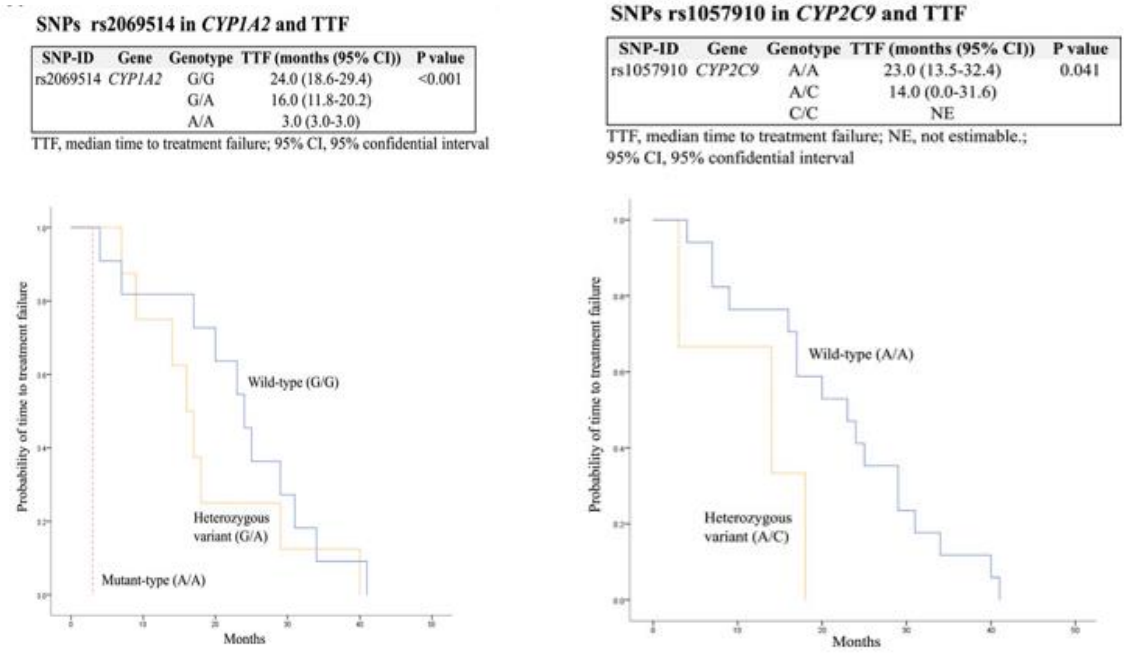
Table 5. Relationship between SNP profiles and clinical endpoints.

SNP ID	Gene	Genotype	All-grade ADRs [n/N (%)]	p-value	ADR Severity [n/N (%)]	p-value	TTF (months, 95% CI)	p-value	PFS (months, 95% CI)	p-value
rs11285 03	ABCB1	G/G	9/9 (100)	0.150	Grade 1–2: 7/9 (77.8)Grade 3: 2/9 (22.2)	0.682	34.0 (34.0–34.0)	0.216	42.0 (42.0–42.0)	0.283
		G/A	28/29 (96.6)		Grade 1–2: 25/28 (89.3)Grade 3: 3/28 (10.7)		21.9 (14.3–29.6)		30.3 (24.7–35.8)	
		A/A	21/25 (84.0)		Grade 1–2: 18/21 (85.7)Grade 3: 3/21 (14.3)		16.6 (11.1–22.1)		30.9 (21.7–40.0)	
rs22311 42	ABCG2	C/C	29/31 (93.5)	0.557	Grade 1–2: 24/29 (82.8)Grade 3: 5/29 (17.2)	0.607	23.9 (17.4–30.3)	0.420	39.0 (31.4–46.6)	0.081
		C/A	25/27 (92.6)		Grade 1–2: 22/25 (88.0)Grade 3: 3/25 (12.0)		16.7 (9.0–24.4)		26.7 (20.3–33.2)	
		A/A	4/5 (80.0)		Grade 1–2: 4/4 (100)Grade 3: 0/4 (0)		21.5 (0.0–46.0)		42.0 (42.0–42.0)	

rs2231164	ABCG2	T/T	17/18 (94.4)	0.669	Grade 1–2: 12/17 (70.6)Grade 3: 5/17 (29.4)	0.055	26.6 (18.3–34.9)	0.128	37.5 (26.7–48.3)	0.287
		T/C	28/30 (93.3)		Grade 1–2: 25/28 (89.3)Grade 3: 3/28 (10.7)		15.4 (9.2–21.6)		30.0 (22.0–34.0)	
		C/C	13/15 (86.7)		Grade 1–2: 13/13 (100)Grade 3: 0/13 (0)		24.2 (12.8–35.6)		39.0 (31.8–46.2)	
rs2622604	ABCG2	C/C	34/38 (89.5)	0.602	Grade 1–2: 29/34 (85.3)Grade 3: 5/34 (14.7)	0.837	19.6 (13.3–26.0)	0.825	30.0 (24.4–35.6)	0.828
		C/T	19/20 (95.0)		Grade 1–2: 17/19 (89.5)Grade 3: 2/19 (10.5)		23.3 (10.6–35.9)		42.0 (42.0–42.0)	
		T/T	5/5 (100)		Grade 1–2: 4/5 (80.0)Grade 3: 1/5 (20.0)		20.0 (14.1–25.9)		NE	
rs4148157	ABCG2	G/G	36/38 (94.7)	0.447	Grade 1–2: 29/36 (80.6)Grade 3: 7/36 (19.4)	0.271	20.9 (15.4–25.4)	0.930	35.7 (28.3–43.0)	0.529
		G/A	19/22 (86.4)		Grade 1–2: 18/19 (94.7)Grade 3: 1/19 (5.3)		19.0 (8.3–29.7)		30.5 (25.2–35.9)	
		A/A	3/3 (100)		Grade 1–2: 3/3 (100)Grade 3: 0/3 (0)		21.5 (0.0–46.0)		42.0 (42.0–42.0)	
rs1871744	ABCG2	T/T	24/27 (88.9)	0.459	Grade 1–2: 20/24 (83.3)Grade 3: 4/24 (16.7)	0.806	16.8 (9.2–24.4)	0.734	35.7 (28.6–42.8)	0.540
		T/C	28/29 (96.6)		Grade 1–2: 25/28 (89.3)Grade 3: 3/28 (10.7)		23.3 (15.9–30.6)		29.1 (23.3–34.9)	
		C/C	6/7 (85.7)		Grade 1–2: 5/6 (83.3)Grade 3: 1/6 (16.7)		27.0 (19.2–34.8)		42.0 (42.0–42.0)	
rs2069514	CYP1A2	G/G	28/31 (90.3)	0.752	Grade 1–2: 23/28 (82.1)Grade 3: 5/28 (17.9)	0.534	24.0 (18.6–29.4)	<0.001[a]	38.4 (33.1–43.7)	0.166
		G/A	25/27 (92.6)		Grade 1–2: 22/25 (88.0)Grade 3: 3/25 (12.0)		16.0 (11.8–20.2)		26.3 (21.4–31.2)	
		A/A	5/5 (100)		Grade 1–2: 5/5 (100)Grade 3: 0/5 (0)		3.0 (3.0–3.0)		22.0 (9.1–34.8)	

n = ADR count within a genotype; N = number of subjects with the genotype; All-grade ADRs and ADR severity (N = 63); TTF = median time to treatment failure (N = 20); PFS = median progression-free survival for patients receiving osimertinib as second-line therapy (N = 36); 95% CI = confidence interval; NE = not estimable.

aDenotes significance.



a) b)

Figure 1. Kaplan–Meier curves and log-rank comparisons illustrating TTF differences associated with (a) CYP1A2 rs2069514 and (b) CYP2C9 rs1057910.

Median PFS was also reduced in carriers of CYP2A6 rs28399433 C/C and CYP2C9 rs1057910 A/C genotypes, with p-values of 0.023 and <0.001, respectively. Among the subset receiving osimertinib as second-line therapy (N = 36), these same SNPs again showed significant associations with shorter PFS (p = 0.001 and 0.010). Details are provided in **Table 6 and Figure 2**.

Table 6. Association between SNPs and clinical outcomes (continued).

SNP ID	Gene	Genotype	All-grade ADRs [n/N (%)]	p-value	ADR Severity [n/N (%)]	p-value	TTF (months, 95% CI)	p-value	PFS (months, 95% CI)	p-value
rs762551	CYP1A2	C/C	3/3 (100)	0.425	Grade 1–2: 2/3 (66.7)Grade 3: 1/3 (33.3)	0.584	NE	0.987	NE	0.539
		C/A	29/33 (87.9)		Grade 1–2: 25/29 (86.2)Grade 3: 4/29 (13.8)		20.5 (15.2–25.7)		30.0 (24.6–35.4)	
		A/A	26/27 (96.3)		Grade 1–2: 23/26 (88.5)Grade 3: 3/26 (11.5)		20.0 (2.2–37.8)		42.0 (42.0–42.0)	
CYP2A6*4	CYP2A6	non*4/non*4	49/54 (90.7)	0.450	Grade 1–2: 42/49 (85.7)Grade 3: 7/49 (14.3)	0.639	21.2 (16.1–26.3)	0.685	34.3 (16.9–52.7)	0.847
		non*4/*4	9/9 (100)		Grade 1–2: 8/9 (88.9)Grade 3: 1/9 (11.1)		15.7 (0.0–33.9)		34.8 (28.5–40.1)	
rs28399433	CYP2A6	A/A	40/43 (93.0)	0.721	Grade 1–2: 34/40 (85.0)Grade 3: 6/40 (15.0)	0.767	18.9 (13.1–26.7)	0.181	33.3 (27.1–39.6)	<0.001*

		A/C	15/17 (88.2)		Grade 1–2: 13/15 (86.7)Grade 3: 2/15 (13.3)		24.3 (15.1–33.6)		42.0 (42.0–42.0)	
		C/C	3/3 (100)		Grade 1–2: 3/3 (100)Grade 3: 0/3 (0)		12.0 (0.0–27.7)		6.0 (6.0–6.0)	
rs1057910	CYP2C9	A/A	53/57 (93.0)	0.563	Grade 1–2: 48/53 (90.6)Grade 3: 5/53 (9.4)	0.003*	23.0 (13.5–32.4)	0.041*	42.0 (42.0–42.0)	0.010*
		A/C	4/5 (80.0)		Grade 1–2: 2/4 (50.0)Grade 3: 2/4 (50.0)		14.0 (0.0–31.6)		24.0 (9.3–38.7)	
		C/C	1/1 (100)		Grade 1–2: 0/1 (0)Grade 3: 1/1 (100)		NE		NE	
rs28371759	CYP3A4	A/A	55/60 (91.7)	0.777	Grade 1–2: 48/55 (87.3)Grade 3: 7/55 (12.7)	0.365	20.4 (15.4–25.4)	NE	34.8 (29.8–39.9)	NE
		A/G	3/3 (100)		Grade 1–2: 2/3 (66.7)Grade 3: 1/3 (33.3)		NE		NE	
rs776746	CYP3A5	A/A	4/5 (80.0)	0.577	Grade 1–2: 4/4 (100)Grade 3: 0/4 (0)	0.690	27.0 (23.1–30.9)	0.835	30.0 (30.0–30.0)	0.356
		A/G	29/31 (93.5)		Grade 1–2: 25/29 (86.2)Grade 3: 4/29 (13.8)		22.5 (14.3–30.7)		37.7 (31.7–43.6)	
		G/G	25/27 (92.6)		Grade 1–2: 21/25 (84.0)Grade 3: 4/25 (16.0)		18.3 (11.1–25.4)		28.6 (21.4–35.9)	
rs1057868	POR	C/C	25/26 (96.2)	0.302	Grade 1–2: 21/25 (84.0)Grade 3: 4/25 (16.0)	0.528	15.8 (6.4–25.2)	0.259	30.0 (19.8–40.2)	0.464
		C/T	26/30 (86.7)		Grade 1–2: 22/26 (84.6)Grade 3: 4/26 (15.4)		21.9 (16.1–27.7)		42.0 (42.0–42.0)	
		T/T	7/7 (100)		Grade 1–2: 7/7 (100)Grade 3: 0/7 (0)		NE		NE	

n = ADR count per genotype; N = genotype total; All-grade ADRs and ADR severity (N = 63); TTF (N = 20); PFS in second-line osimertinib users (N = 36); 95% CI = confidence interval; NE = not estimable.

aIndicates statistical significance.

SNPs rs28399433 in CYP2A6 and PFS

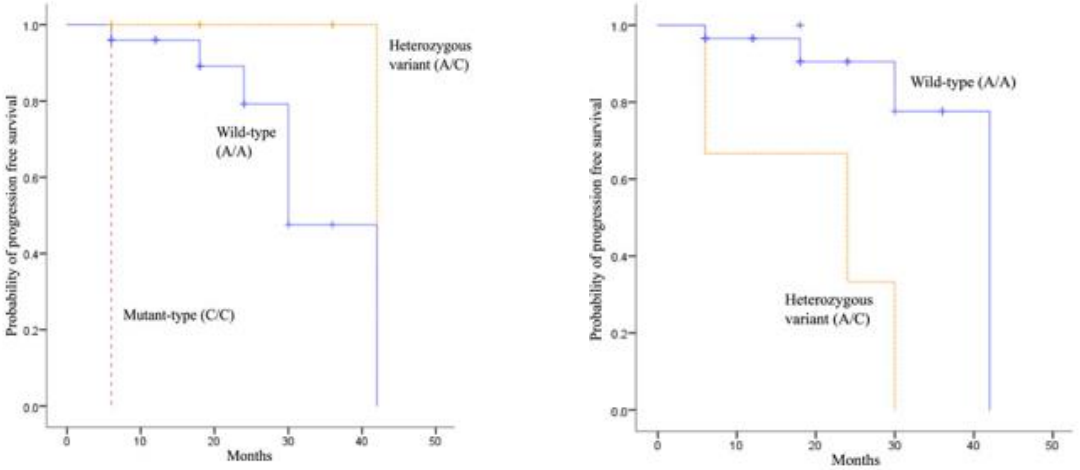
SNP-ID	Gene	Genotype	PFS (months (95% CI))	P value
rs28399433	*CYP2A6*	A/A	33.3 (27.1-39.6)	< 0.001*
		A/C	42.0 (42.0-42.0)	
		C/C	6.0 (6.0-6.0)	

PFS, median progression-free survival; 95% CI, 95% confidential interval

SNPs rs1057910 in CYP2C9 and PFS

SNP-ID	Gene	Genotype	PFS (months (95% CI))	P value
rs1057910	*CYP2C9*	A/A	42.0 (42.0-42.0)	0.010*
		A/C	24.0 (9.3-38.7)	
		C/C	NE	

PFS, median progression-free survival; NE, not estimable.; 95% CI, 95% confidential interval



a) b)

Figure 2. Kaplan–Meier visualizations and log-rank tests illustrating PFS trends among patients receiving second-line osimertinib: (a) CYP2A6 rs28399433 and (b) CYP2C9 rs1057910.

Incidence of ADRs

Table 7 outlines the overall ADR profile. Six patients (9.5%) required temporary treatment interruption, and seventeen (27.0%) needed dose reductions due to toxicity. Specific ADRs leading to dose adjustment included diarrhea (4 patients, 6.3%), acneiform rash (3 patients, 4.8%), neutropenia (3 patients, 4.8%), thrombocytopenia (1 patient, 1.6%), bullous dermatitis (1 patient, 1.6%), myositis (1 patient, 1.6%), transaminitis (1 patient, 1.6%), QTc prolongation (1 patient, 1.6%), mucositis (1 patient, 1.6%), and alopecia (1 patient, 1.6%).

Dose-modification strategies consisted of: 80 mg every other day (10 patients, 15.9%), 80 mg three times weekly (5 patients, 7.9%), 80 mg five times weekly (1 patient, 1.6%), and 40 mg once daily (1 patient, 1.6%).

Table 7. Incidence rates of adverse drug reactions.

Adverse Event	Total Incidence, All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Acneiform rash	29 (46.0)	15 (23.8)	13 (20.6)	1 (1.6)
Dry skin	23 (36.5)	20 (31.7)	3 (4.8)	0 (0)
Diarrhea	17 (27.0)	11 (17.4)	3 (4.8)	3 (4.8)
QTc prolongation	14 (22.2)	7 (11.1)	3 (4.8)	4 (6.3)
Dry eye	12 (19.0)	11 (17.5)	1 (1.6)	0 (0)
Paronychia	8 (12.7)	6 (9.5)	2 (3.2)	0 (0)
Thrombocytopenia	8 (12.7)	7 (11.1)	1 (1.6)	0 (0)
Mucositis	7 (11.1)	5 (7.9)	2 (3.2)	0 (0)
Transaminitis	5 (7.9)	4 (6.3)	1 (1.6)	0 (0)
Anemia	5 (7.9)	4 (6.3)	1 (1.6)	0 (0)
Neutropenia	4 (6.3)	0 (0)	4 (6.3)	0 (0)
Urticaria	2 (3.2)	1 (1.6)	1 (1.6)	0 (0)
Alopecia	1 (1.6)	0 (0)	1 (1.6)	0 (0)
Bullous dermatitis	1 (1.6)	0 (0)	1 (1.6)	0 (0)
Papulopustular rash	1 (1.6)	0 (0)	0 (0)	1 (1.6)
Paroxysmal atrial fibrillation	1 (1.6)	0 (0)	1 (1.6)	0 (0)

Nausea/vomiting	1 (1.6)	1 (1.6)	0 (0)	0 (0)
Anorexia	1 (1.6)	1 (1.6)	0 (0)	0 (0)
Myalgia	1 (1.6)	1 (1.6)	0 (0)	0 (0)
Myositis	1 (1.6)	0 (0)	0 (0)	1 (1.6)

A population pharmacokinetic analysis previously demonstrated that osimertinib exposure—quantified through AUC values of the parent compound and its two active metabolites, AZ5104 and AZ7550—rises proportionally with the likelihood of developing ADRs [12]. AZ5104 is notably more potent, showing roughly an eight-fold increase in activity against EGFR variants [11]. Although AZ5104 and AZ7550 comprise only about 10% of the parent drug [12], reported decreases of 10%–23% in AZ5104 AUC among Asian versus Caucasian populations may influence therapeutic outcomes.

Furthermore, data from Asian cohorts have identified significant associations between ABCB1 rs1128503 and ABCG2 rs2231137 and grade ≥2 osimertinib-related toxicities [15]. Despite these insights, the relationship between specific SNPs and osimertinib's therapeutic performance remains insufficiently understood, and the exact polymorphisms that modulate osimertinib pharmacokinetics and clinical behavior in NSCLC have yet to be fully defined.

This investigation represents the first attempt to examine a broad panel of genetic variants across genes implicated in the pharmacokinetics of osimertinib, allowing simultaneous evaluation of therapeutic benefit and safety outcomes. All observed allele distributions adhered to Hardy–Weinberg expectations [20]. In this cohort, the rate of dose reduction was 27.0%, exceeding the 16.5% reported in the AURA 3 trial, and the overall occurrence of ADRs surpassed those observed in FLAURA, AURA2, and AURA3 [13, 21, 22]. These discrepancies may stem from genetic variability between enrolled populations; in the cited trials, Asian participants receiving osimertinib composed only 62%, 63%, and 65% of the respective study groups. For instance, the ABCG2 rs2231164 (C) loss-of-function allele appears at 23.72% in South Asians but only 12.12% in Europeans [23]. Likewise, the CYP2A6*4 reduced-function allele shows notable interethnic differences [24], likely contributing to elevated osimertinib exposure in Thai individuals. Such genetic disparities may explain the contrasts in ADR frequency and dose modification between our analysis and earlier clinical trials. Furthermore, the ORR in our study was 49.2%, which is below the 71% documented in AURA 3 [22]. Divergence in treatment lines may underlie this difference: in AURA 3, osimertinib was used as second-line therapy in 96% of cases and as later-line therapy in 4%, whereas in our dataset, 57.1% received it in the second-line setting and 27.0% in later lines.

We identified six SNPs with significant associations with ADR development: rs2231142 in ABCG2 (A/A), rs2622604 in ABCG2 (T/T), CYP2A6 heterozygous variant (non*4/*4), rs1057910 in CYP2C9 (C/C), rs28371759 in CYP3A4 (A/G), and rs762551 in CYP1A2 (C/C). These results align with past work linking genotype and ADR susceptibility. For example, ABCG2 rs2231142 (A/A) has been tied to severe thrombocytopenia with sunitinib [25], while rs2622604 (T/T) is linked to irinotecan-related severe myelosuppression [26]. Likewise, the CYP2A6 (*4) allele has been associated with letrozole-related toxicities [27], and CYP3A4 *18 (G) influences tacrolimus-induced ADRs [28]. Notably, unlike other loci, rs762551 in CYP1A2 (C/C) demonstrated a significant relationship with osimertinib-induced ADRs. This may reflect the fact that CYP1A2 activity increases in the presence of inducers such as tobacco exposure or substantial caffeine intake, resulting in higher enzyme activity in the A/A variant and correspondingly lower ADR incidence [29, 30]. Regarding treatment response, we identified two SNPs—rs2069514 in CYP1A2 and rs1057910 in CYP2C9—that correlated with median TTF, and two others—rs28399433 in CYP2A6 and rs1057910 in CYP2C9—that correlated with median PFS. Importantly, rs1057910 in CYP2C9 was linked to ADRs, TTF, and PFS simultaneously.

The variants identified in CYP450 enzymes and efflux transporter genes showed significant relationships with ADR occurrence, TTF, and PFS. Since osimertinib undergoes metabolism and transport via CYP450 pathways as well as ABCB1 and ABCG2 [10], genetic differences in these systems could alter how the drug is handled and distributed within the body. Based on this, we proposed that reduced-function alleles in CYP450, ABCB1, or ABCG2 might influence the tissue penetration and accumulation of osimertinib. Prior animal data indicate that ABCB1 and ABCG2 contribute to tissue buildup of several TKIs [31]. Because AZ5104, the active metabolite of osimertinib, demonstrates stronger activity against EGFR mutations than the parent molecule [7] and represents roughly 10% of the osimertinib concentration [12], excess accumulation of the parent drug could raise ADR rates while simultaneously shortening both TTF and PFS. As an illustration, SNP rs1057910 (C) in CYP2C9 produces

a leucine residue at position 359 and is designated CYP2C9*3, a reduced-activity allele [32]. Individuals with this genotype may display impaired clearance of osimertinib, resulting in higher systemic exposure that elevates ADR risk but also limits the availability of AZ5104, thus worsening survival metrics.

These observations parallel earlier research on exposure–response behavior for osimertinib, where elevated drug levels were linked to an increased mortality rate [33]. Higher systemic concentrations were also associated with a greater likelihood of rash, diarrhea, or QTc prolongation, and prior work has demonstrated a linear connection between osimertinib concentrations and adverse event development [12]. Mechanistically, EGFR-TKI toxicities arise from suppressed EGFR1 and EGFR2 (HER2) activity, which disrupts epithelial growth and repair in tissues that express these receptors. This leads to changes in keratinocyte turnover, impaired gastrointestinal epithelial recovery, and alterations in myocyte growth [34–36].

Several constraints should be acknowledged. The cohort was relatively small, and some clinical variables were retrieved retrospectively. Nonetheless, all genotype frequencies were consistent with Hardy–Weinberg expectations [20], and medical information was validated by treating physicians. Another limitation was the inability to fully adjust for other factors, such as adherence to therapy, though pill counts performed by oncology pharmacists indicated 100% compliance at each visit. No drug interactions affecting osimertinib exposure were identified. However, coffee intake was not controlled, which could influence enzyme activity in carriers of rs762551 in CYP1A2 (A/A), an inducible variant associated with decreased ADR risk when exposure to inducers like heavy caffeine intake is present [29, 30]. Finally, this study did not include a pharmacokinetic assessment, although the SNP–outcome associations observed were consistent with prior literature.

Conclusion

In summary, we identified several key SNPs linked to higher ADR rates, shorter TTF, and reduced PFS among Thai patients with NSCLC receiving osimertinib. These results highlight the potential value of incorporating pharmacogenetic information to tailor therapy for individuals with EGFR-mutated NSCLC. Larger investigations incorporating direct measurements of osimertinib and AZ5104 exposure will be needed to validate these conclusions.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. doi:10.3322/caac.21660
2. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. J Thorac Oncol. 2022;17(3):362–87. doi:10.1016/j.jtho.2021.11.003
3. Detarkom S, Incharoen P, Jinawat A, Trachu N, Kamprerasart K, Prasongsook N, et al. Tumor heterogeneity and molecular profile of NSCLC in Thai population. J Thorac Oncol. 2018;13(10):S949–50. doi:10.1016/j.jtho.2018.08.1777
4. Westover D, Zugazagoitia J, Cho B, Lovly C, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol. 2018;29(Suppl 1):i10–9. doi:10.1093/annonc/mdx703
5. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013;19(8):2240–7. doi:10.1158/1078-0432.CCR-12-2246

6. Li Y, Mao T, Wang J, Zheng H, Hu Z, Cao P, et al. Toward the next generation EGFR inhibitors: an overview of osimertinib resistance mediated by EGFR mutations in non-small cell lung cancer. Cell Commun Signal. 2023;21(1):71. doi:10.1186/s12964-023-01082-8
7. Remon J, Steuer C, Ramalingam SS, Felip E. Osimertinib and other third-generation EGFR TKI in EGFR-mutant NSCLC patients. Ann Oncol. 2018;29(Suppl 1):i20–7. doi:10.1093/annonc/mdx704
8. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced non-small cell lung cancer. N Engl J Med. 2020;382(1):41–50. doi:10.1056/NEJMoa1913662
9. Dickinson PA, Cantarini MV, Collier J, Frewer P, Martin S, Pickup K, et al. Metabolic disposition of osimertinib in rats, dogs, and humans: insights into a drug designed to bind covalently to a cysteine residue of epidermal growth factor receptor. Drug Metab Dispos. 2016;44(8):1201–12. doi:10.1124/dmd.115.069203
10. AstraZeneca. TAGRISSO (osimertinib) [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2021
11. Han L, Zhang X, Wang Z, Zhang X, Zhao L, Fu W, et al. SH-1028, an irreversible third-generation EGFR TKI, overcomes T790M-mediated resistance in non-small cell lung cancer. Front Pharmacol. 2021;12(1):665253. doi:10.3389/fphar.2021.665253
12. Brown K, Comisar C, Witjes H, Maringwa J, de Greef R, Vishwanathan K, et al. Population pharmacokinetics and exposure–response of osimertinib in patients with non-small cell lung cancer. Br J Clin Pharmacol. 2017;83(6):1216–26. doi:10.1111/bcp.13223
13. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. N Engl J Med. 2018;378(2):113–25. doi:10.1056/NEJMoa1713137
14. Cho BC, Chewaskulyong B, Lee KH, Dechaphunkul A, Sriuranpong V, Imamura F, et al. Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset. J Thorac Oncol. 2019;14(1):99–106. doi:10.1016/j.jtho.2018.09.004
15. Ishikawa E, Yokoyama Y, Chishima H, Kasai H, Kuniyoshi O, Kimura M, et al. Population pharmacokinetics, pharmacogenomics, and adverse events of osimertinib and its two active metabolites, AZ5104 and AZ7550, in Japanese patients with advanced non-small cell lung cancer: a prospective observational study. Invest New Drugs. 2023;41(1):122–33. doi:10.1007/s10637-023-01328-9
16. Liao D, Liu Z, Zhang Y, Liu N, Yao D, Cao L, et al. Polymorphisms of drug-metabolizing enzymes and transporters contribute to the individual variations of erlotinib steady state trough concentration, treatment outcomes, and adverse reactions in EGFR-mutated non-small cell lung cancer patients. Front Pharmacol. 2020;11(1):664. doi:10.3389/fphar.2020.00664
17. Sogawa R, Nakashima C, Nakamura T, Takeuchi K, Kimura S, Komiya K, et al. Association of genetic polymorphisms with afatinib-induced diarrhoea. In Vivo. 2020;34(3):1415–9. doi:10.21873/invivo.11922
18. Suzumura T, Kimura T, Kudoh S, Umekawa K, Nagata M, Matsuura K, et al. Reduced CYP2D6 function is associated with gefitinib-induced rash in patients with non-small cell lung cancer. BMC Cancer. 2012;12(1):568. doi:10.1186/1471-2407-12-568
19. Ngamjarus C. n4Studies: sample size calculation for an epidemiological study on a smart device. Siriraj Med J. 2016;68(3):160-70.
20. PharmGKB. PharmGKB [Internet]. 2021.
21. Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2016;17(12):1643–52. doi:10.1016/S1470-2045(16)30508-3
22. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum–pemetrexed in EGFR T790M–positive lung cancer. N Engl J Med. 2017;376(7):629–40. doi:10.1056/NEJMoa1612674
23. Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, et al. An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2021;110(3):563–72. doi:10.1002/cpt.2350
24. Pang C, Liu JH, Xu YS, Chen C, Dai PG. The allele frequency of CYP2A6*4 in four ethnic groups of China. Exp Mol Pathol. 2015;98(3):546–8. doi:10.1016/j.yexmp.2015.03.040

25. Low SK, Fukunaga K, Takahashi A, Matsuda K, Hongo F, Nakanishi H, et al. Association study of a functional variant on ABCG2 gene with sunitinib-induced severe adverse drug reaction. PLoS One. 2016;11(2):e0148177. doi:10.1371/journal.pone.0148177
26. Cha PC, Mushiroda T, Zembutsu H, Harada H, Shinoda N, Kawamoto S, et al. Single nucleotide polymorphism in ABCG2 is associated with irinotecan-induced severe myelosuppression. J Hum Genet. 2009;54(10):572–80. doi:10.1038/jhg.2009.80
27. Desta Z, Kreutz Y, Nguyen AT, Li L, Skaar T, Kamdem LK, et al. Plasma letrozole concentrations in postmenopausal women with breast cancer are associated with CYP2A6 genetic variants, body mass index, and age. Clin Pharmacol Ther. 2011;90(5):693–700. doi:10.1038/clpt.2011.174
28. Bruckmueller H, Werk AN, Renders L, Feldkamp T, Tepel M, Borst C, et al. Which genetic determinants should be considered for tacrolimus dose optimization in kidney transplantation? A combined analysis of genes affecting the CYP3A locus. Ther Drug Monit. 2015;37(3):288–95. doi:10.1097/FTD.0000000000000142
29. Djordjevic N, Ghotbi R, Jankovic S, Aklillu E. Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2 −163C>A polymorphism. Eur J Clin Pharmacol. 2010;66(7):697–703. doi:10.1007/s00228-010-0823-4
30. Wang L, Hu Z, Deng X, Wang Y, Zhang Z, Cheng ZN. Association between common CYP1A2 polymorphisms and theophylline metabolism in non-smoking healthy volunteers. Basic Clin Pharmacol Toxicol. 2013;112(4):257–63. doi:10.1111/bcpt.12038
31. Al-Shammari AH, Masuo Y, Fujita KI, Yoshikawa Y, Nakamichi N, Kubota Y, et al. Influx and efflux transporters contribute to the increased dermal exposure to active metabolite of regorafenib after repeated oral administration in mice. J Pharm Sci. 2019;108(6):2173–9. doi:10.1016/j.xphs.2019.01.018
32. ClinVar–NCBI. VCV000008408.12 [Internet]. 2013.
33. Rodier T, Puszkiel A, Cardoso E, Balakirouchenane D, Narjoz C, Arrondeau J, et al. Exposure–response analysis of osimertinib in patients with advanced non-small cell lung cancer. Pharmaceutics. 2022;14(9):1844. doi:10.3390/pharmaceutics14091844
34. Giovannini M, Gregorc V, Belli C, Roca E, Lazzari C, Viganò MG, et al. Clinical significance of skin toxicity due to EGFR-targeted therapies. J Oncol. 2009;2009(1):849051. doi:10.1155/2009/849051
35. Hirsh V, Blais N, Burkes R, Verma S, Croitoru K. Management of diarrhea induced by epidermal growth factor receptor tyrosine kinase inhibitors. Curr Oncol. 2014;21(6):329–36. doi:10.3747/co.21.2241
36. Ikebe S, Amiya R, Minami S, Ihara S, Higuchi Y, Komuta K. Osimertinib-induced cardiac failure with QT prolongation and torsade de pointes in a patient with advanced pulmonary adenocarcinoma. Int Cancer Conf J. 2020;10(1):68–71. doi:10.1007/s13691-020-00450-2