

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 AUC_{0–24}, 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/ μ L, 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)	≥ 3 rd-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	non4/non4	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	non4/non4	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
rs1128503	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)	
rs2231142	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

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					Grade 1–2: 25/28 (89.3)		15.4 (9.2– 21.6)		30.0 (22.0– 34.0)	
	T/C	28/30 (93.3)			Grade 3: 3/28 (10.7)					
					Grade 1–2: 13/13 (100)		24.2 (12.8– 35.6)		39.0 (31.8– 46.2)	
	C/C	13/15 (86.7)			Grade 3: 0/13 (0)					
rs26226 04	ABCG2	C/C	34/38 (89.5)	0.602	Grade 1–2: 29/34 (85.3)	0.837	19.6 (13.3– 26.0)	0.825	30.0 (24.4– 35.6)	0.828
					Grade 3: 5/34 (14.7)					
					Grade 1–2: 17/19 (89.5)		23.3 (10.6– 35.9)		42.0 (42.0– 42.0)	
	C/T	19/20 (95.0)			Grade 3: 2/19 (10.5)					
					Grade 1–2: 4/5 (80.0)		20.0 (14.1– 25.9)		NE	
	T/T	5/5 (100)			Grade 3: 1/5 (20.0)					
rs41481 57	ABCG2	G/G	36/38 (94.7)	0.447	Grade 1–2: 29/36 (80.6)	0.271	20.9 (15.4– 25.4)	0.930	35.7 (28.3– 43.0)	0.529
					Grade 3: 7/36 (19.4)					
					Grade 1–2: 18/19 (94.7)		19.0 (8.3– 29.7)		30.5 (25.2– 35.9)	
	G/A	19/22 (86.4)			Grade 3: 1/19 (5.3)					
					Grade 1–2: 3/3 (100)		21.5 (0.0– 46.0)		42.0 (42.0– 42.0)	
	A/A	3/3 (100)			Grade 3: 0/3 (0)					
rs18717 44	ABCG2	T/T	24/27 (88.9)	0.459	Grade 1–2: 20/24 (83.3)	0.806	16.8 (9.2– 24.4)	0.734	35.7 (28.6– 42.8)	0.540
					Grade 3: 4/24 (16.7)					
					Grade 1–2: 25/28 (89.3)		23.3 (15.9– 30.6)		29.1 (23.3– 34.9)	
	T/C	28/29 (96.6)			Grade 3: 3/28 (10.7)					
					Grade 1–2: 5/6 (83.3)		27.0 (19.2– 34.8)		42.0 (42.0– 42.0)	
	C/C	6/7 (85.7)			Grade 3: 1/6 (16.7)					
rs20695 14	CYP1A 2	G/G	28/31 (90.3)	0.752	Grade 1–2: 23/28 (82.1)	0.534	24.0 (18.6– 29.4)	<0.001 ^a	38.4 (33.1– 43.7)	0.166
					Grade 3: 5/28 (17.9)					
					Grade 1–2: 22/25 (88.0)		16.0 (11.8– 20.2)		26.3 (21.4– 31.2)	
	G/A	25/27 (92.6)			Grade 3: 3/25 (12.0)					
					Grade 1–2: 5/5 (100)		3.0 (3.0–3.0)		22.0 (9.1– 34.8)	
	A/A	5/5 (100)			Grade 3: 0/5 (0)					

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.

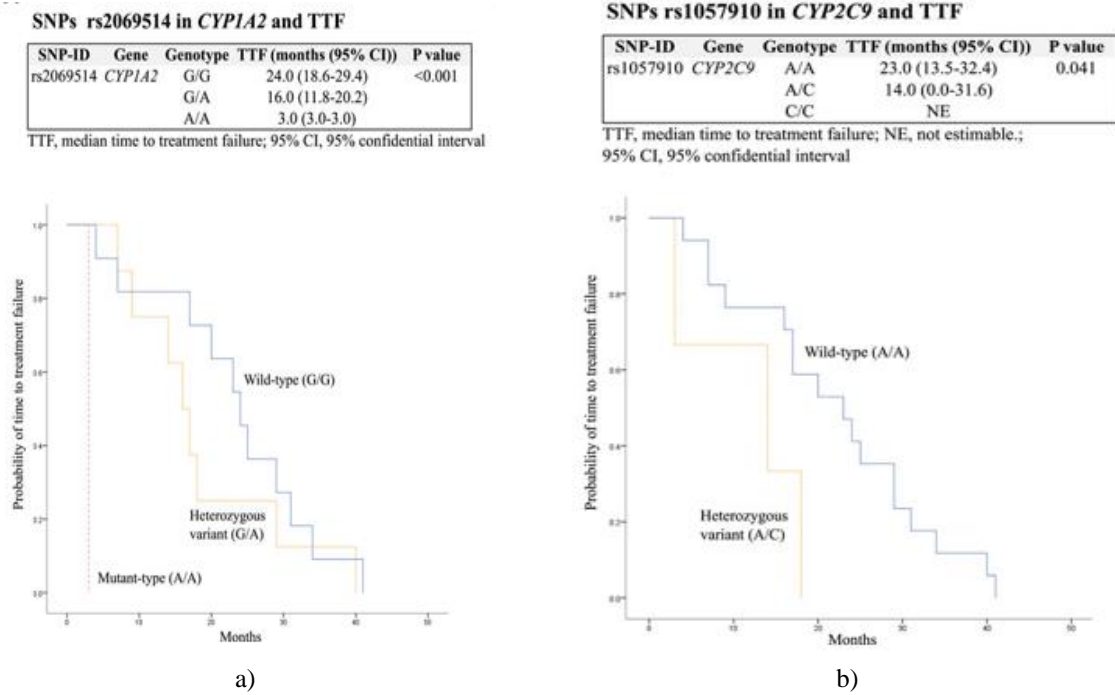


Figure 1. Kaplan–Meier curves and log-rank comparisons illustrating TTF differences associated with (a) CYP1A2 rs2069514 and (b) CYP2C9 rs1057910.

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		ADR Severity		TTF		PFS	
			ADRs [n/N (%)]	p-value	[n/N (%)]	p-value	(months, 95% CI)	p-value	(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)		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	non4/non4	49/54 (90.7)	0.450	Grade 1–2: 42/49 (85.7)Grade 3: 7/49 (14.3)		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)	
rs2839943 3	CYP2A6	A/A	40/43 (93.0)	0.721	Grade 1–2: 34/40 (85.0)Grade 3: 6/40 (15.0)		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		24.3 (15.1–33.6)		42.0 (42.0–42.0)	

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					(86.7)Grade 3: 2/15 (13.3)					
		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	
rs2837175 9	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

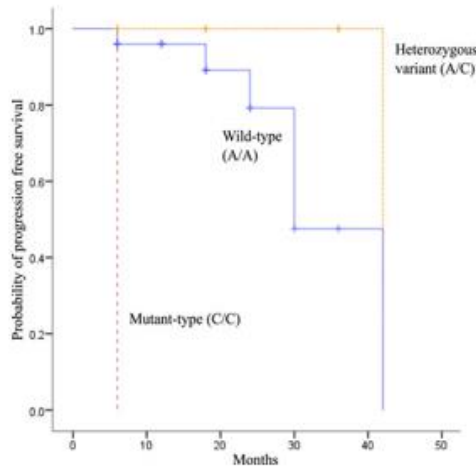
SNP-ID	Gene	Genotype	PFS (months (95% CI))	P value
rs28399433	CYP2A6	A/A	33.3 (27.1-39.6)	< 0.001*
		A/C	42.0 (42.0-42.0)	
		C/C	6.0 (6.0-6.0)	

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

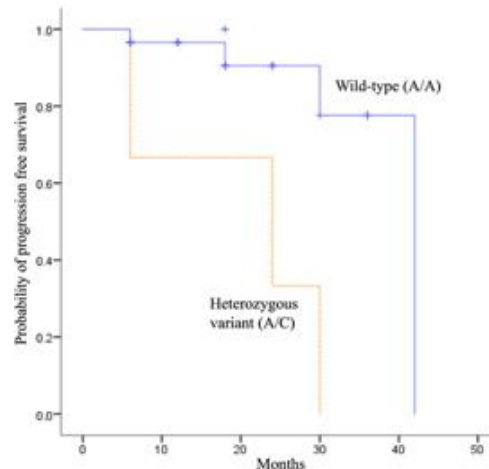
SNPs rs1057910 in CYP2C9 and PFS

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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