

Supplementary

# Comparison of Resistance Spectra After First and Second Line Osimertinib Treatment Detected by Liquid Biopsy

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**Table S1.** Patient treatment and alterations detected with liquid biopsy in the 56 patient's cohort of late stage NSCLC during disease progression under TKI treatment. (X) mutation present from a single nucleotide change; (XX) mutation present from two nucleotide changes leading to C797S: (c.2389T>A and c.2390G>C) ; *TP53* in bold letter because of *RB1* mutations suggesting a small-cell transformation SCLC. Abbreviations: erlotinib (ERL), gefitinib (GEF), rociletinib (ROC), afatinib (AFA), osimertinib (OSI). Varaiant of unknown significance (VUS).

patient	EGFR driver confirmed by liquid biopsy	TKI received	EGFR dependent resistance			EGFR Independent Putative Resistance					Passenger Mutation	
			T790M	C797S	other	amplification	SCLC/SC C switch	kinase switch	fusion	alternate pathway	(in)activating	VUS
P15	E746_A750del	OSI		X							<i>TP53</i> (R110L)	<i>PIK3CA</i> (K111del)
P55	L858R	OSI			T854A	<i>MET</i>			<i>ALK-EML4</i> (v3)		<i>TP53</i> (R248Q)	<i>MET</i> (A179T)
P29	L858R	OSI					<i>RB1</i> (R787*)				<i>STK11</i> (L105*); <b><i>TP53</i></b> (G244V)	
P27	L858R	OSI									<i>TP53</i> (E336fs*10)	<i>KEAP1</i> (E134K)
P43	L858R	OSI									<i>BRCA2</i> (E2981fs); <i>TP53</i> (Y234C)	<i>ALK</i> (R1084H); <i>PDGFRA</i> (R829*)
P46	L861Q	OSI										<i>BRCA1</i> (I562V)
P49	E709G, G719S	OSI									<i>TP53</i> (R156P, E298*)	<i>TSC2</i> (I723V); <i>ATM</i> (E586_G587delinsDC, A425V); <i>FGFR3</i> (E330Q); <i>CTNNB1</i> (K435N)
P20	non	OSI										
P30	non	OSI										
P44	E746_S752delins V	ERL, OSI	loss of		G724S							<i>ATM</i> (K3004E)
P16	E746_S752delins V	AFA, OSI, CRI	loss of			<i>EGFR</i>	<i>RB1</i> fusion (intergenic)				<b><i>TP53</i></b> (Q167*); <i>STK11-STK11</i> (I231M); <i>TSC2</i> (D1406N)	<i>CTNNB1</i> (I231M); <i>TSC2</i> (D1406N)
P51	E746_A750del	AFA, OSI	loss of			<i>MET</i>					<i>TP53</i> (R175H)	<i>ROS1</i> (R448H)
P14	L858R	ERL, OSI	loss of			<i>MET</i>						<i>FGFR1</i> (R749H)
P32	E746_A750del	AFA, OSI	loss of					<i>ERBB2</i> (V777L, I767M, S310Y)		<i>KRAS</i> (G13D)	<i>BRCA2</i> (T3030fs, N2134fs); <i>TP53</i> (R249S)	

Genetic Alterations in Lung Adenocarcinoma											
Patient ID	Primary Alteration	Secondary Alterations	Copy Number Changes	Gene Expression	Protein Expression	Pathway Analysis	Therapeutic Implications	Prognostic Markers	Response to Therapy	Survival Outcome	Notes
P37	E746_A750del	ERL, OSI	loss of			RET-RUFY1	PIK3CA (E545K, E542K)	TP53 (Q136P)	EGFR (R932C); PIK3CA (R87T)		
P06	E746_A750del	AFA, OSI	loss of				KRAS (G12D)	ATR (R2148*); TP53 (W91*)	ATR (H1520R); MTOR (D2512Y, R2505*); RET (A641T)		
P42	E746_A750del	AFA, OSI	loss of				PIK3CA (E545K)	CDKN2A fusion (intergenic)	ERBB2 (T216M)		
P41	E746_A750del	AFA, OSI	loss of					TP53 (Q192*)			
P19	L747_S752del	ERL, AFA, OSI	loss of						MTOR (M2366V)		
P04	K745_A750delins K	ERL, OSI	loss of					TP53 (R158P)			
P17	L747_T751delins P	GEF, AFA, OSI	loss of						PDGFRA (E336G)		
P11	E746_A750del	GEF, OSI	loss of								
P38	E746_A750del	GEF, OSI	loss of						ALK (P230Q), TSC2 (R905Q)		
P35	L858R	AFA, OSI	X	X	L718V, L718Q, L792H, G796S	EGFR		TP53 (c.376-2A>T)	FGFR3 (D760N); TSC2 (R1451S); BRCA1 (K556N)		
P31	L747_P753delins S	GEF, ERL, AFA, OSI	X	X		EGFR					
P08	L858R	ERL, OSI	X	X		RB1 (G203fs)		TP53 (E198*)			
P12	L858R	ERL, OSI	X	X			ERBB2 (S310F)		ALK (G35fs)		
P23	L858R	AFA, OSI	X	X			AGK-BRAF (S37Y)	CTNNB1 (S37Y)			
P56	L747_P753delins S	AFA, OSI	X	X			DLG1-BRAF (S37Y)	IDH2 (R140Q); TP53 (Q104*, S241F)	EGFR (M1002T)		
P13	E746_T751delins A	AFA, OSI	X	X			CTNNB1 (S37Y)	TP53 (G199V)			
P33	E746_A750del	AFA, OSI	X	X			MTOR (Y1974H)		ATM (H1352Q)		
P24	L747_T751delins P	AFA, OSI	X	X				TP53 (R248Q)			
P02	K745_A750delins K	AFA, ROC, OSI	X	X					TSC1 (A659V)		
P18	E746_A750del	ERL, OSI	X	X				TP53 (V157F)	EGFR (G459A)		
P39	E746_A750del	GEF, OSI	X	X				CTNNB1 (S37Y)	ATM (N1719D)		
P03	K745_A750delins K	ERL, OSI	X	XX	V843I	EGFR	KRAS (A146V)		DDR2 (S215F), ROS1 (I595del)		
P05	E746_A750del	ERL, ROC, OSI	X	XX			TACC-FGF R3		TSC1 (R992T)		
P48	E746_A750del	AFA, OSI	X	XX				TP53 (R158L)			
P28	E746_A750del	AFA, OSI	X	XX					ARAF (G499E), MET (M1247T), TP53 (I162N)		
P36	L858R	ERL, OSI	X		L718Q	MET	RB1	TP53 (V73fs)			

					(S114fs, c.1960+1G >A)		
P54	L858R	AFA, OSI	X	L792H	RET (V804L)	TP53 (I254N)	
P07	L858R	AFA, OSI	X				
P22	E746_A750del	AFA, OSI	X	ATR (S2264L), ATM NFE2L2 (c.2921+1G>T) (L266F), EGFR (R962C)			
P34	E746_A750del	AFA, OSI	X	TP53 (R248Q)			
P01	L747_P753delins Q	ERL, OSI	X	ATM (R3008H)			
P21	L858R	GEF, OSI, AFA	X	TP53 (V216L) ERBB2 (D1252N)			
P10	E746_A750del	AFA, GEF, ERL, OSI		PTEN (S399fs)	TP53 (H179Y)	MTOR (R731H)	
P52	E746_A750del	AFA, GEF, OSI		TP53 (R249G)			
P26	E746_A750del	AFA, OSI					
P45	E709V, G719C	ERL, OSI		TP53 (I195N,W53*)			
P53	non	AFA, GEF, OSI					
P09	non	AFA, OSI					
P47	non	AFA, OSI					
P50	non	AFA, OSI					
P40	non	ERL, OSI					
P25	non	GEF, OSI					