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Supplementary Materials: Targeting BRAF Activation as Acquired Resistance Mechanism to EGFR Tyrosine Kinase Inhibitors in EGFR-Mutant Non-Small-Cell Lung Cancer

Frank Aboubakar Nana [1,2] and Sebahat Ocak

Table S1. Main clinical trials performed with third-generation EGFR tyrosine kinase inhibitors and BRAF +/- MEK inhibitors in advanced-stage NSCLC.

Compound	Company	Clinica trial															Drugs No Longer in Active Clinical Development
caption	caption	Phase	Clinical Trials.gov identifier	Name	Indication	N	Drugs	ORR, % (95% CI)	OR (95% CI)	*P* value	Median PFS, Months (95% CI)	HR (95% CI)	*P* value	Median OS, Months (95% CI)	HR (95% CI)	P value	Recruitment Status	References	caption
Third-generation EGFR TKIs																			
Abivertinib or avitinib (AC0010)	Hangzhou ACEA Pharmaceutical Research Co.	1	NCT02330367		*EGFR*+ NSCLC, after previous EGFR TKI	52	Abivertinib 50, 100, 200, 350, 500, 550, 600 mg BID (RP2D: 300 mg BID)	36.5									Unknown	[1]	
		2	NCT03300115		*EGFR* T790M+ NSCLC, after previous EGFR TKI	222	Abivertinib 300 mg BID										Unknown		
		3	NCT03058094	AEGIS-1	*EGFR* T790M+ NSCLC, after previous EGFR TKI	0	Arm 1: Abivertinib 300 mg BID										Withdrawn		
							Arm 2: Cisplatin-pemetrexed												
Alflutinib (AST2818)	Shanghai Allist Pharmaceuticals	1	NCT02973763		*EGFR*+ NSCLC, after	14	Alflutinib 20, 40, 80,	50.0									Active, not recruiting	[2]	

					previous EGFR TKI		160, 240 mg QD							
		1/2	NCT03127449		*EGFR*+ NSCLC, after previous EGFR TKI	116	Alflutinib 80, 160 mg QD (RP2D: 80 mg QD)	76.7 (68.0–84.1)				11.1 (9.6-NR)	Active, not recruiting	[2]	
		2	NCT03452592	ALSC003	*EGFR* T790M+ NSCLC, after previous EGFR TKI	220	Alflutinib 80 mg QD	74.1 (67.8–79.7)				9.6 (8.2–9.7)	Unknown	[3]	
Almonertinib (HS-10296)	Jiangsu Hansoh Pharmaceutical Co.	1	NCT02981108		*EGFR*+ (including T790M+) NSCLC, after previous EGFR TKI	120	Almonertinib 55, 110, 220, 260 mg QD (RP2D: 110 mg QD)	50 (41–59) overall, 52 (42–63) in 94 patients with T790M+	9.6 (8.3–11.1), 11.0 (9.5-NR) in 94 patients with T790M+				Unknown	[4]	
		2	NCT02981108	APOLLO	*EGFR*+ (including T790M+) NSCLC, after previous EGFR TKI	244	Almonertinib 110 mg QD	68.9 (62.2–74.2)	12.3 (9.6–13.8)						
Lazertinib (YH25448)	Yuhan Coporation	1/2	NCT03046992		*EGFR*+ NSCLC, after previous EGFR TKI	127	Lazertinib 20, 40, 80, 120, 160, 240, 320 QD (RP2D: 240 mg QD)	54 (46–63)					Active, not recruiting	[5]	
Naquotinib (ASP8273)	Astellas Pharma	3	NCT02588261	SOLAR	*EGFR*+ NSCLC, 1L treatment	530	Arm 1: Naquotinib 300 mg QD	33 (27.4–39.0)	9.3 (5.6–11.1)	1,611	0.992		Terminated	[6]	Stopped in 2017 due to lower efficacy than osimertinib
							Arm 2: Gefitinib 250 mg daily or erlotinib 150 mg QD	47.9 (41.7–54.1)	9.6 (8.8-NE)						
Nazartinib (EGF-816)	Novartis Oncology	1/2	NCT02108964	CEGF816X2101	*EGFR*+ NSCLC, ≥ 1L treatment	180	Nazartinib 75, 100, 150, 200, 225, 300, 350 mg QD (RP2D: 150 mg QD)	51 (43–59)	9.1 (7.3–11.1)				Active, not recruiting	[7]	Stopped in 2018 due to lower efficacy and higher toxicity than osimertinib

Olmutinib (HM61713/BI 1482694)	Hanmi Pharmaceutical	1/2	NCT01588145		*EGFR* T790M+ NSCLC, after previous EGFR TKI	272	Olmutinib 300 mg QD, 500 mg BID, 800 mg QD (RP2D: 800 mg QD)	55.1 (42.6–67.1)			6.9 (5.6-9.7)			NR			Completed	[8]	Stopped in 2016 because of two cases of toxic epidermal necrolysis, one of them fatal
Osimertinib (AZD9291)	Astra Zeneca	1	NCT01802632	AURA	*EGFR* T790M+ NSCLC, after previous EGFR TKI	253	Osimertinib 20 mg QD and then escalation to 240 mg QD according to tolerance	61 (52–70) in patients with T790M+, 21 (12–34) in patients with T790M- who could be evaluated			9.6 (8.3-NR) in patients with T790M+, 2.8 (2.1–4.3) in patients with T790M-						Active, not recruiting	[9]	
		2	NCT01802632	AURA	*EGFR* T790M+ NSCLC, after previous EGFR TKI	201	Osimertinib 20, 40, 80, 160, 240 mg QD (RP2D: 80 mg QD)	62 (54–68)			12.3 (9.5–13.8)						Active, not recruiting	[10]	
		1/2	NCT01802632	AURA	*EGFR*+ NSCLC, 1L treatment	60	Osimertinib 80 or 160 mg QD	77 (64–87)			20.5 (15.0–26.1)						Active, not recruiting	[11]	
		2	NCT02094261	AURA2	*EGFR* T790M+ NSCLC, after previous EGFR TKI	210	Osimertinib 80 mg QD	70 (64–77)			9.9 (8.5–12.3)						Active, not recruiting	[12]	
		3	NCT02151981	AURA3	*EGFR* T790M+ NSCLC, after previous EGFR TKI	279	Arm 1: Osimertinib 80 mg QD	71 (65–76)	5.39 (3.47–8.48)	< 0.001	10.1	0.30 (0.23-0.41)	< 0.001	26.8 (23.5–31.5)	0.87 (0.67–1.12)	0.277	Active, not recruiting	[13,14]	
							Arm 2: Platinum-pemetrexed	31 (24–40)			4.4			22.5 (20.2–28.8)					
		3	NCT02296125	FLAURA	*EGFR*+ NSCLC, 1L treatment	556	Arm 1: Osimertinib 80 mg QD	80 (75–85)	1.27 (0.85–1.90)	0.24	18.9	0.46 (0.37–0.57)	< 0.001	38.6 (34.5-41.8)	0.80 (0.64-1.00)	0.046	Active, not recruiting	[15,16]	

						Arm 2: Gefitinib 250 mg QD or erlotinib 150 mg QD	76 (70–81)	10.2	31.8 (26.6–36)			
Rezivertinib (BPI-7711)	Beta Pharma Inc.	1	NCT03386955		*EGFR* T790M+ NSCLC, after previous EGFR TKI	82 Rezivertinib 30, 60, 120, 180, 240, 300 mg QD (RP2D: 180 mg QD)	54.5 (30–55)				Active, not recruiting	[17]
		2	NCT03812809		*EGFR* T790M+ NSCLC, after previous EGFR TKI	226 Rezivertinib 180 mg QD					Active, not recruiting	
Rociletinib (CO-1686)	Clovis Oncology	1/2	NCT01526928	TIGER-X	*EGFR* T790M+ NSCLC, after previous EGFR TKI	130 Rociletinib 150 mg QD to 900 mg BID (RP2D: 625 mg BID)	59 (45–73) in 46 patients with T790M+, 29 (8–51) in 17 patients with T790M- who could be evaluated				Terminated	[18]	Stopped in 2016 due to lower efficacy and higher toxicity than osimertinib
TAS-121	Taiho Pharmaceutical	1	NCT02274337		*EGFR*+ NSCLC, after previous EGFR TKI	134 TAS-121 4, 8, 10, 12, 16 mg QD	28 in patients with T790M+, 19 in patients with T790M-					[19]	Stopped in 2018 due to lower efficacy than osimertinib
BRAF +/- MEK kinase inhibitors												
Dabrafenib (GSK-2118436) + trametinib (GSK1120212)	GlaxoSmithKline	2	NCT01336634		*BRAF* V600E+ NSCLC, after previous 1 to 3L chemotherapy	57 Dabrafenib 150 mg BID + trametinib 2 mg QD	63.2 (43.3–75.6)	9.7 (6.9–19.6)	Immature		Active, not recruiting	[20]	
		2	NCT01336634		*BRAF* V600E+	36 Dabrafenib 150 mg	64 (46–79)	10.9 (7.0–16.6)	24.6 (12.3-NE)		Completed	[21]	

				NSCLC, 1L treatment	BID+ trametinib 2 mg QD					
Vemurafenib (RO5185426, PLX4032)	Roche and Plexxicon	2	NCT01524978	*BRAF* V600+ NSCLC, ≥ 1L treatment	62	Vemurafenib 360 mg BID	37.1 (25.2–50.3) overall, 37.5 (8.5–75.5) in previously untreated patients, 37.0 (24.3–51.3) in previously treated patients	6.5 (5.29.0)	15.4 (9.6–22.8)	Completed [22]

Table S2. Main clinical trials ongoing or planned with third- or fourth-generation EGFR tyrosine kinase inhibitors and BRAF + MEK inhibitors in advanced-stage NSCLC.

Compound	Company	Clinical trial						
caption	caption	Phase	Clinical Trials.gov identifier	Name	Indication	N estimated	Drugs	Recruitement status
Third-generation EGFR TKIs								
Abivertinib (AC0010)	Hangzhou ACEA Pharmaceutical Research Co.	3	NCT03856697	AEGIS-2	*EGFR*+ NSCLC, 1L treatment	406	Arm 1: Abivertinib 300 mg BID Arm 2: Gefitinib 250 mg QD	Not yet recruiting
Alflutinib (AST2818)	Shanghai Allist Pharmaceuticals	3	NCT03787992	FLAG	*EGFR*+ NSCLC, 1L treatment	358	Arm 1: Alflutinib 80 mg QD Arm 2: Gefitinib 250 mg QD	Active, not recruiting
Almonertinib (HS-10296)	Jiangsu Hansoh Pharmaceutical Co.	3	NCT03849768		*EGFR*+ NSCLC, 1L treatment	350	Arm 1: Almonertinib 110 mg QD Arm 2: Gefitinib 250 mg QD	Recruiting
		3	NCT04500704	ACROSS 1	*EGFR*+ NSCLC with other co-occurring driver mutations, 1L treatment	166	Arm 1: Almonertinib 110 mg QD Arm 2: Almonertinib 110 mg QD+ 4 to 6 cycles of carboplatin-pemetrexed followed by pemetrexed maintenance	Not yet recruiting
		3	NCT04500717	ACROSS 2	*EGFR*+ NSCLC with co-occurring tumor suppressor genes (P53, RB1, PTEN), 1L treatment	460	Arm 1: Almonertinib 110 mg QD Arm 2: Almonertinib 110 mg QD + 4 to 6 cycles of carboplatin-pemetrexed followed by pemetrexed maintenance	Not yet recruiting
ASK120067	Jiangsu Aosaikang Pharmaceutical Co.	1/2	NCT03502850		*EGFR* T790M+ NSCLC, after previous EGFR TKI	507	ASK120067 40,80,160,240,320,480 mg QD	Recruiting
		3	NCT04143607		*EGFR*+ NSCLC, 1L treatment	334	Arm 1: ASK120067 160 mg BID Arm 2: Gefitinib 250 mg QD	Recruiting

D-0316	Beta Pharmaceuticals Co.	1	NCT03452150		*EGFR*+ NSCLC, after previous EGFR TKI	50	D-0316 QD, escalation according to tolerance	Active, not recruiting
		2	NCT03861156		*EGFR* T790M+ NSCLC, after previous EGFR TKI	286	D-0316 75 mg QD, escalation to 100 mg QD according to tolerance	Active, not recruiting
		2/3	NCT04206072		*EGFR*+ NSCLC, 1L treatment	360	Arm 1: D-0316 75 mg QD for first cycle and then escalation to 100 mg QD according to tolerance Arm 2: Icotinib 125 mg TID	Active, not recruiting
Lazertinib (YH25448)	Yuhan Coporation	3	NCT04248829	LASER301	*EGFR*+ NSCLC, 1L treatment	380	Arm 1: Lazertinib 240 mg QD Arm 2: Gefitinib 250 mg QD	Recruiting
		3	NCT04487080	MARIPOSA	*EGFR*+ NSCLC, 1L treatment	1000	Arm 1: Lazertinib 240 mg QD + amivantamab (IV) (1050 mg if < 80 kg and 1400 mg if ≥ 80 kg in 28-day cycles: once weekly in cycle 1 (split dose on days 1-2) and then every 2 weeks) Arm 2: Lazertinib 240 mg QD + matching osimertinib placebo Arm 3: Osimertinib 80 mg QD + matching lazertinib placebo	Recruiting
Osimertinib (AZD9291)	Astra Zeneca	3	NCT04035486	FLAURA2	*EGFR*+ NSCLC, 1L treatment	586	Arm 1: Osimertinib 80 mg QD Arm 2: Osimertinib 80 mg QD + 4 cycles of platinum-pemetrexed followed by pemetrexed maintenance	Recruiting
Rezivertinib (BPI-7711)	Beta Pharma Inc.	3	NCT03866499	RAZOR	*EGFR*+ NSCLC, 1L treatment	294	Arm 1: Rezivertinib 180 mg QD Arm 2: Gefitinib 250 mg QD	Recruiting
SH-1028	Nanjing Sanhome Pharmaceutical Co.	1	NCT03603262		*EGFR*+ NSCLC, after previous EGFR TKI	85	SH-1028 starting dose 60 mg QD. If tolerated subsequent cohorts will test increasing doses: 100,200,300,400 mg QD	Unknown
		2	NCT03823807		*EGFR* T790M+ NSCLC, after previous EGFR TKI	300	SH-1028 100 mg QD	Unknown
		3	NCT04239833		*EGFR*+ NSCLC, 1L treatment	245	Arm 1: SH-1028 200 mg QD Arm 2: Gefitinib 250 mg QD	Not yet recruiting

Fourth-generation EGFR TKIs								
BLU-945	Blueprint Medicines	1/2	NCT04862780	SYMPHONY	*EGFR* T790M and C797S+ NSCLC, after previous EGFR TKI	120	BLU-945, escalation according to tolerance	Recruiting
BRAF + MEK kinase inhibitors								
Dabrafenib (GSK-2118436) + trametinib (GSK1120212)	GlaxoSmithKline	2	NCT03543306	BRF113928	*BRAF* V600E+ NSCLC, after previous 1 to 2L chemotherapy	27	Dabrafenib 150 mg BID + trametinib 2 mg QD	Recruiting
Encorafenib (LGX818) + binimetinib (ARRY-162)	Novartis, Array Biopharma	2	NCT03915951		*BRAF* V600E+ NSCLC, ≥ 1L treatment	90	Encorafenib 450 mg QD + binimetinib 45 mg BID	Recruiting

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