

Mechanisms of Acquired Resistance and ctDNA Clearance in EGFR-Mutated Advanced NSCLC Following Lazertinib Treatment: Results From the Phase 3 LASER301 Study

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CONCLUSIONS

- In evaluable patients with EGFR-mutated locally advanced or metastatic NSCLC who were treated with lazertinib in LASER301, EGFR-dependent pathway alterations were observed in 16% of patients, with EGFR C797S being the most common alteration. In the EGFR-independent pathway, alterations were identified in 43% of patients, with TP53 and PIK3CA alterations being the most frequently observed
- Patients without detectable EGFR driver mutations at disease progression exhibited lower rates of detectable acquired resistance
- There was no clear correlation between the type of mechanism of acquired resistance and treatment duration
- Baseline germline analysis of patients with suboptimal treatment response revealed the difference in the frequency of ATM or KIT alterations
- In patients with detectable EGFR-mutated ctDNA at baseline, ctDNA clearance was achieved in the majority (94%) of patients by Week 6 (Cycle 3 Day 1)

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INTRODUCTION

- Lazertinib is a central nervous system-penetrant, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) approved for the treatment of EGFR-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) in the Republic of Korea¹⁻³
 - In the United States and European Union, lazertinib is approved in combination with amivantamab for the first-line treatment of locally advanced or metastatic NSCLC with EGFR mutations (exon 19 deletion [Ex19Del] or exon 21 L858R substitution [L858R])^{4,5}
- Patients with treatment-naïve, EGFR-mutated advanced NSCLC who received lazertinib in the LASER301 study had significantly longer median progression-free survival (PFS) versus those who received the first-generation TKI gefitinib (20.6 vs 9.7 months, respectively; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.34-0.58; P < 0.001)⁶
 - In the phase 3 MARIPOSA study, patients with EGFR-mutated advanced NSCLC who were treated with first-line amivantamab + lazertinib demonstrated a significant improvement in overall survival compared with patients who were treated with osimertinib (HR, 0.75; 95% CI, 0.61-0.92; P < 0.005)⁷
- Previously demonstrated acquired resistance to treatment with first-generation EGFR TKIs⁸ warranted an exploratory analysis of mechanisms of acquired resistance in LASER301, which could impact the response of patients who are treated with lazertinib

OBJECTIVE

- We report results of the mechanisms of acquired resistance and circulating tumor DNA (ctDNA) clearance in patients who received lazertinib in LASER301

METHODS

Study Design

- In LASER301, patients with treatment-naïve, EGFR-mutated (Ex19Del or L858R) locally advanced or metastatic NSCLC were included
- Patients were randomly assigned 1:1 to receive lazertinib (240 mg daily) or gefitinib (250 mg daily)
- Additional details on the methods for LASER301 have been previously reported⁶

Alterations Acquired at Disease Progression

- To evaluate the emergence of potential resistance mechanisms, next-generation sequencing (NGS; Guardant360; Guardant Health) of circulating cell-free DNA was performed on paired blood samples collected at baseline and at disease progression from patients who received lazertinib and who had both detectable plasma EGFR mutations at baseline and ctDNA results at disease progression
 - Acquired, non-synonymous, characterized mutations that were detected in a sample at disease progression (but not in the screening sample) were considered putative mechanisms of resistance, excluding genes and/or alterations with unknown clinical or functional significance

ctDNA Clearance

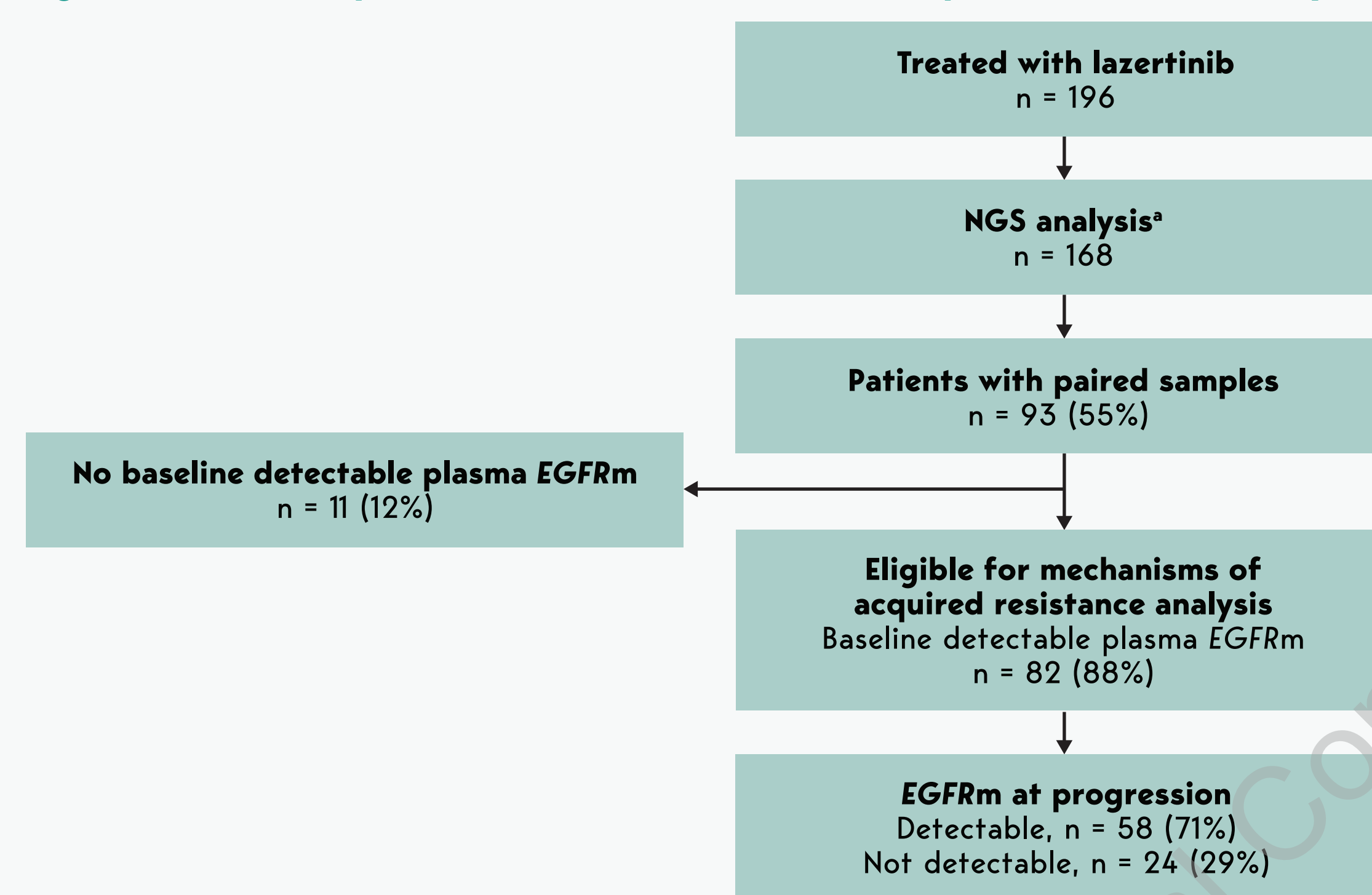
- To evaluate ctDNA clearance, Ex19Del and L858R ctDNA in the blood were analyzed at baseline and Week 6 (Cycle 3 Day 1) with a droplet digital PCR-based EGFR mutation test (Droplex EGFR Mutation Test v2; Gencurix)
- ctDNA clearance was defined as undetectable EGFR mutations at Week 6 in patients with detectable EGFR-mutated ctDNA at baseline

RESULTS

Alterations Acquired at Disease Progression

- The NGS analysis included 168 patients, of whom 82 patients had detectable plasma EGFR mutations at baseline and were eligible for the mechanisms of acquired resistance analysis at disease progression
 - Among the patients who were eligible for the mechanisms of acquired resistance analysis, EGFR mutations were detected in 58 patients at disease progression (Figure 1)

Figure 1. Patient Disposition for the Mechanisms of Acquired Resistance Analysis



EGFRm, epidermal growth factor receptor mutation; NGS, next-generation sequencing. *NGS was analyzed using Guardant360.

- The acquired resistance analysis subset exhibited baseline characteristics that were generally similar to those observed in the overall population treated with lazertinib in LASER301 (Table 1)

Table 1. Patient Demographic Characteristics of the Overall Population Treated With Lazertinib and the Acquired Resistance Analysis Subset

	Overall population treated with lazertinib (n = 196)	Acquired resistance analysis subset (n = 82)
Median (range) age, y	67 (31-87)	65 (33-82)
Sex, n (%)		
Female	132 (67)	54 (66)
Male	64 (33)	28 (34)
Race, n (%)		
Asian	129 (66)	64 (78)
Non-Asian	67 (34)	18 (22)
EGFR mutation at random assignment, ^a n (%)		
Ex19Del	122 (62)	55 (67)
L858R	74 (38)	27 (33)
CNS metastases at study entry, n (%)	51 (26)	29 (35)
Overall disease classification, ^b n (%)		
Metastatic	191 (97)	81 (99)
Locally advanced	5 (3)	1 (1)
Cancer stage at enrollment, n (%)		
IIIB	3 (2)	0
IIIC	2 (1)	1 (1)
IIVA	86 (44)	31 (38)
IIVB	105 (54)	50 (61)
Smoking status, n (%)		
Never	135 (69)	58 (71)
Former	50 (26)	19 (23)
Current	11 (6)	5 (6)
WHO performance status score, n (%)		
0	49 (25)	16 (20)
1	147 (75)	66 (80)

CNS, central nervous system; EGFR, epidermal growth factor receptor; Ex19Del, exon 19 deletion; L858R, exon 21 L858R substitution; WHO, World Health Organization. ^aMutation status at randomization was confirmed by local or central laboratory testing. ^bOverall disease classification was derived from the cancer stage and metastatic lesion information at enrollment.

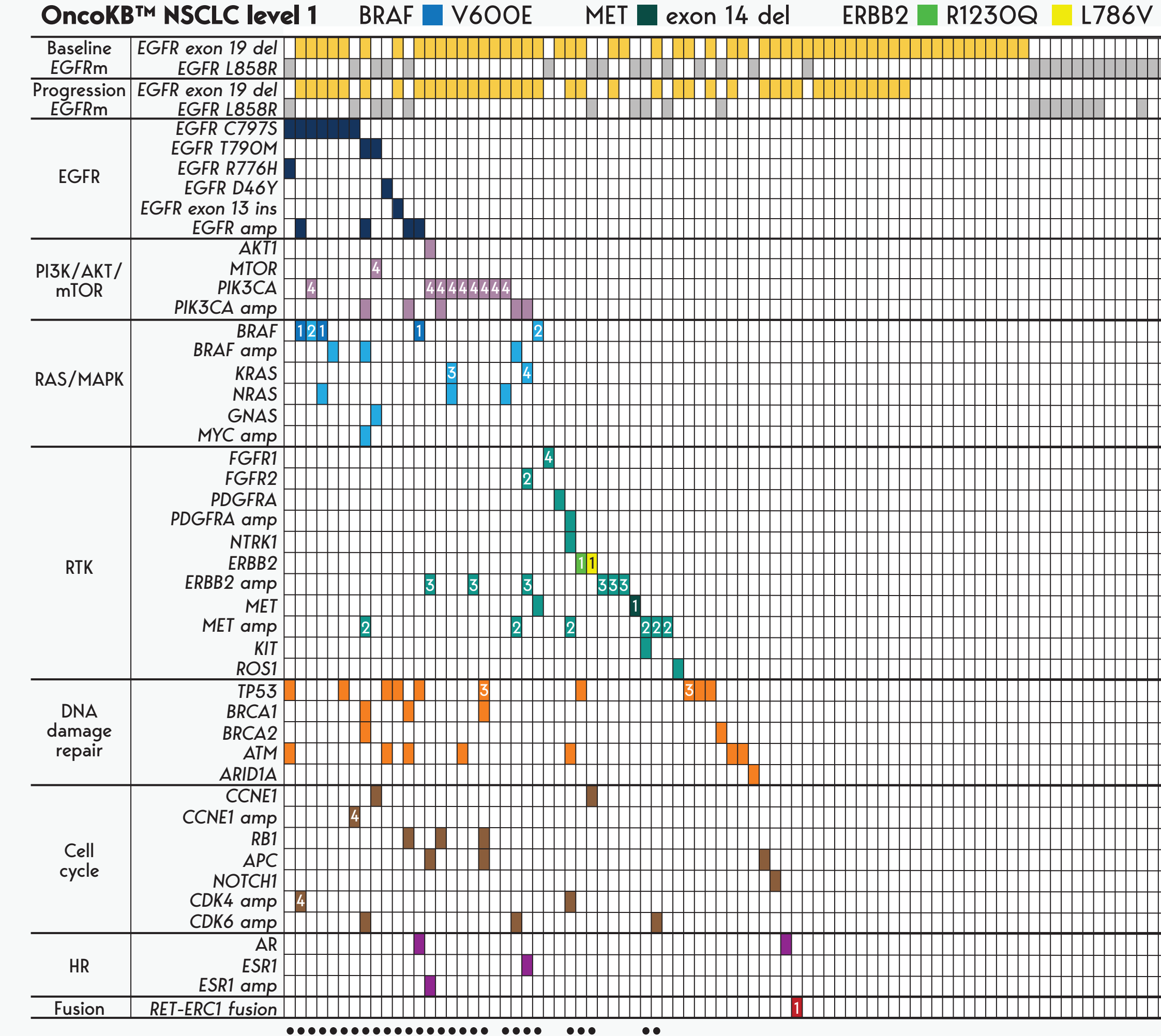
- A total of 48/82 patients (59%) had acquired resistance alterations at disease progression. EGFR-dependent pathway alterations were observed in 13/82 patients (16%), while EGFR-independent pathway alterations accounted for 35/82 patients (43%)
 - The most common alteration in the EGFR-dependent pathway was EGFR C797S (7 patients [9%])
 - In the EGFR-independent pathway, alterations were identified in DNA damage-repair genes in 18 patients (22%), in the receptor tyrosine kinase (RTK) pathway in 19 patients (23%), and in the RAS/RAF pathway in 12 patients (15%); ERBB2 and MET alterations were identified in 8 patients (9%) each (Table 2)
- Among patients who had acquired resistance alterations at disease progression, the frequency of complex resistance (defined as the presence of ≥2 acquired resistance mutations) was 28/48 (58%; Figure 2)
- At disease progression, the detection rate of an EGFR driver mutation (Ex19Del or L858R) was 58/82 patients (71%; Figure 2)

Table 2. Alterations Acquired at Disease Progression Following Treatment With Lazertinib (n = 82)

Pathway and category	Alteration	n (%)	
EGFR-dependent pathway	EGFR C797S	7 (9)	
	EGFR T790M	2 (2)	
	EGFR R776H	1 (1)	
	EGFR D46Y	1 (1)	
	EGFR exon 13/28+ ins	1 (1)	
	EGFR amp	4 (5)	
EGFR-independent pathways	AKT1	1 (1)	
	MTOR	1 (1)	
	PIK3CA	9 (11)	
	PIK3CA amp	5 (6)	
	BRAF	5 (6)	
	BRAF amp	3 (4)	
	KRAS	3 (4)	
	NRAS	3 (4)	
	GNAS	1 (1)	
	MYC amp	1 (1)	
	FGFR1	1 (1)	
	FGFR2	1 (1)	
	PDGFRA	1 (1)	
	PDGFRA amp	1 (1)	
	NTRK1	1 (1)	
PI3K alterations	ERBB2	2 (2)	
	ERBB2 amp	6 (7)	
	MET	2 (2)	
	MET amp	6 (7)	
	KIT	1 (1)	
	ROS1	1 (1)	
	TP53	10 (12)	
	BRCA1	3 (4)	
	BRCA2	2 (2)	
	ATM	7 (9)	
RAS/RAF alterations	ARID1A	1 (1)	
	CCNE1	2 (2)	
	CCNE1 amp	1 (1)	
	RBT	3 (4)	
	APC	3 (4)	
	NOTCH1	1 (1)	
	CDK4 amp	2 (2)	
	CDK6 amp	3 (4)	
	AR	2 (2)	
	ESR1	1 (1)	
Cell cycle gene alterations	ESR1 amp	1 (1)	
	RET fusion ERCT	1 (1)	
	Acquired fusion alterations	RET fusion ERCT	1 (1)

amp, amplification; EGFR, epidermal growth factor receptor; ins, insertion; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RTK, receptor tyrosine kinase.

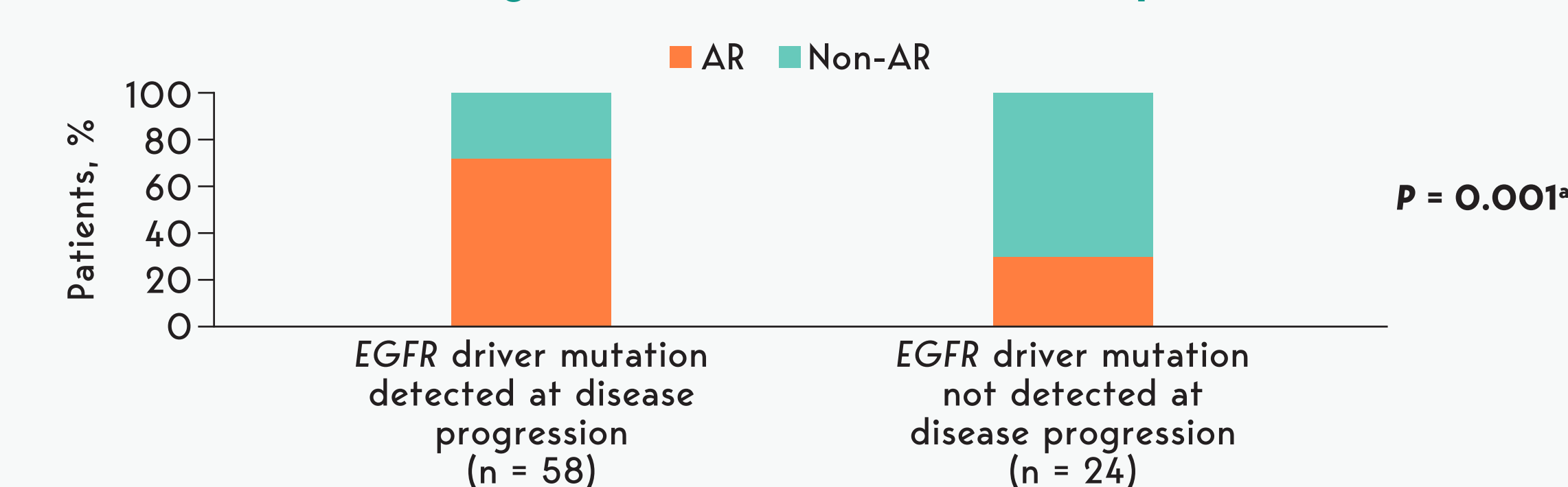
Figure 2. Acquired Mutations Following Treatment With Lazertinib



amp, amplification; del, deletion; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; FDA, US Food and Drug Administration; HR, hormone receptor; ins, insertion; L858R, exon 21 L858R substitution; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RTK, receptor tyrosine kinase. The black dots along the bottom of the figure indicate patients with complex acquired resistance, which was defined as having ≥2 acquired resistance alterations. The numbers in the cells indicate the OncoKB™ oncogenic-evidence levels, which are defined as follows: Level 1, FDA-recognized biomarker predictive of response to an FDA-approved drug for this indication; Level 2, Standard-of-care biomarker recommended by the NCCN or other expert panels, predictive of response to an FDA-approved drug for this indication; Level 3A, Compelling clinical evidence supporting the biomarker as predictive of the response to a drug for this indication, but neither the biomarker nor the drug are standards of care; Level 4, Compelling biologic evidence supporting the biomarker as predictive of the response to a drug, but neither the biomarker nor the drug are standards of care.

- 41/58 patients (70%) with an EGFR driver mutation detected at disease progression had detectable acquired resistance, while only 7/24 patients (29%) without an EGFR driver mutation detected at disease progression had detectable acquired resistance (Figure 3)
- The variant allele fraction (VAF) of EGFR detected at disease progression was numerically lower than at baseline (data not shown). Specifically, the median VAF of Ex19Del declined from 11.3 to 2.0, and L858R showed a reduction from 5.4 to 3.1

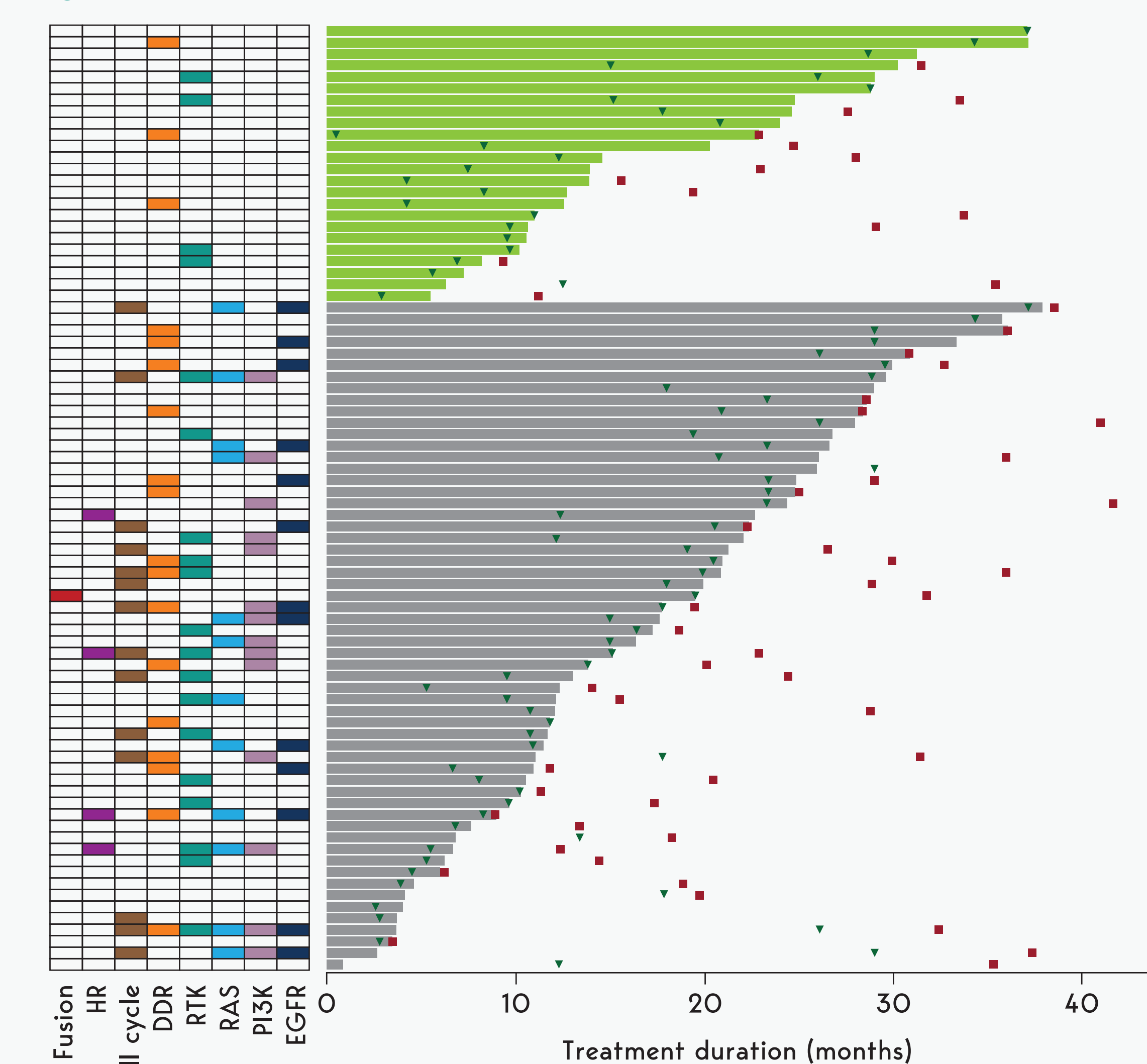
Figure 3. Proportion of Patients With or Without EGFR Driver Mutations Detected at Disease Progression Who Had Detectable Acquired Resistance



AR, acquired resistance; EGFR, epidermal growth factor receptor. *P value calculated using Fisher's exact test.

- In the resistance analysis subset, no clear relationship was observed between the type of mechanism of acquired resistance and treatment duration (Figure 4)

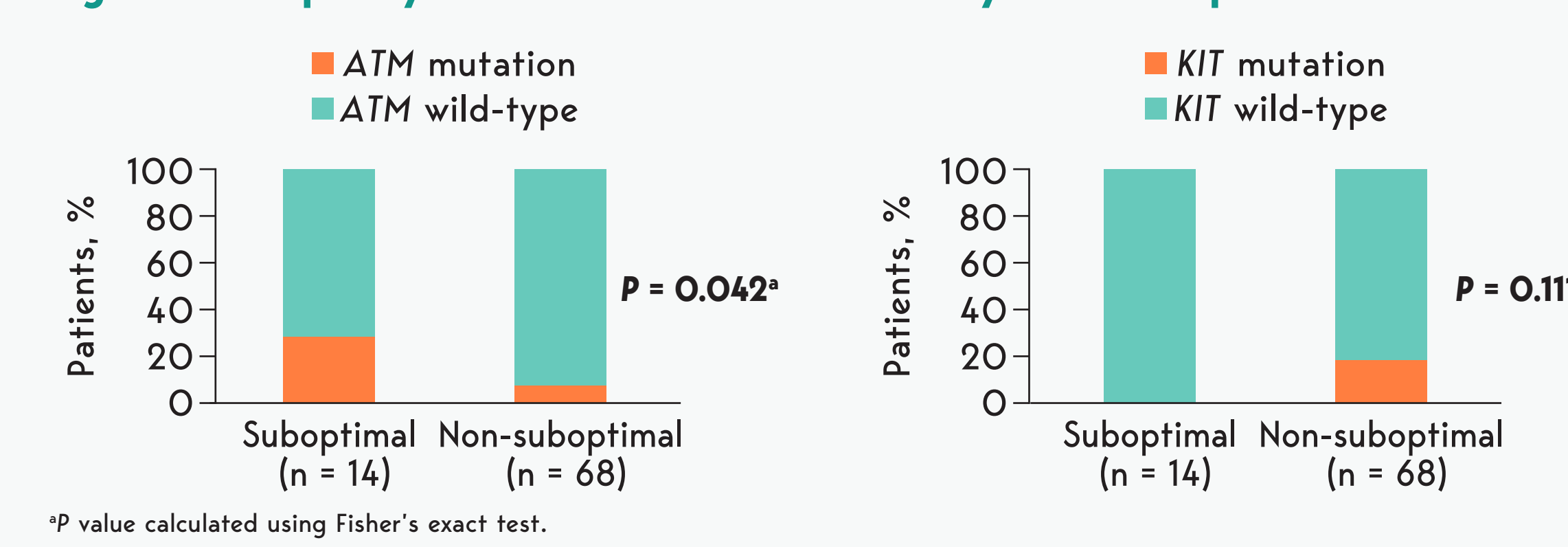
Figure 4. Duration of Treatment by Candidate Resistance Mechanisms



EGFR driver mutation not detected at disease progression (green square), EGFR driver mutation detected at disease progression (grey square), Death (red square). DDD, DNA damage response; EGFR, epidermal growth factor receptor; HR, hormone receptor; PI3K, phosphatidylinositol 3-kinase; RAS, rat sarcoma virus; RTK, receptor tyrosine kinase.

- A suboptimal response to treatment was defined by either progressive disease with a PFS of <6 months or non-clearance of plasma ctDNA at 6 weeks (as measured by droplet digital PCR)
- The comparison of baseline genomic characteristics between the suboptimal and non-suboptimal groups showed a difference in the frequency of ATM or KIT alterations (Figure 5)

Figure 5. Frequency of ATM and KIT Alterations by Tumor Response Status



*P value calculated using Fisher's exact test.

ctDNA Clearance

- In total, 149 patients were included in the ctDNA clearance analysis
 - At baseline, ctDNA was detected in 77/149 patients (52%), with Ex19Del detected in 49/77 patients (64%) and L858R detected in 28/77 patients (36%)
 - At Week 6, ctDNA was cleared in 72/77 patients (94%)
 - Among the patients included in the NGS analysis, ctDNA clearance was also analyzed in 69/82 patients (84%). Among them, EGFR mutations were detected at baseline in 50 patients and ctDNA clearance at Week 6 was observed in 47 patients