Tumor invasiveness, response to ALK inhibitors and resistance mechanism in non-small cell lung cancer(NSCLC) with different ALK variants

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Background

Scholars have made much progress on the investigation about tumor invasiveness, response to ALK inhibitors and resistance mechanism in different ALK variants, however, these studies have reached inconsistent conclusions.

Objective

We conducted this research with relatively larger sample size to make more comprehensive analysis for different ALK variants.

Methods

Medical records of patients with advanced ALK+ NSCLC who received first-line alectinib or crizotinib were retrospectively collected in our center. Shorter EML4 variants included EML4 fusions up to exon 6 and longer EML4 variants contained EML4 fusions at least exon 13.

Cohort 1: first-line alectinib n=61

Cohort 2: first-line crizotinib n=59

Results

Figure 1a+1b: Distribution of ALK variants

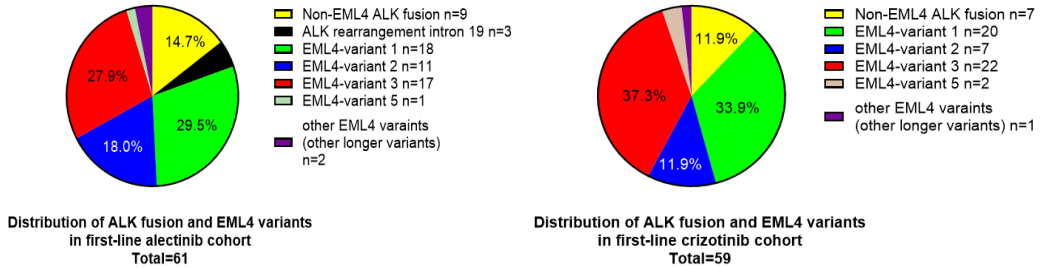


Table 1: ECOG and tumor invasiveness between patients with EML4 shorter or longer variants

	Shorter forms n=42	Longer forms n=59	P value
ECOG			
0-1	30(71.4%)	46(77.8%)	P=0.453
≥2	12(28.6%)	13(22.0%)	
Extra-thoracic metastases			
Yes	28(66.7%)	42(71.2%)	P=0.627
No	14(33.3%)	17(28.8%)	
CNS metastases			
Yes	6(14.3%)	11(18.6%)	P=0.564
No	36(85.7%)	48(81.4%)	
Liver metastases			
Yes	8(19.0%)	10(16.9%)	P=0.786
No	34(81.0%)	49(83.1%)	
Bone metastases			
Yes	15(35.7%)	27(45.8%)	P=0.313
No	27(64.3%)	32(54.2%)	
Distant organs involved			
≤2	32(76.2%)	42(71.2%)	P=0.575
≥3	10(23.8%)	17(28.8%)	

Table 2a:ORR between shorter and longer variants in patients with target lesions in first-line alectinib cohort

	Shorter forms n=16	Longer forms n=22	P value
Radiological evaluation			
CR+PR	12(75%)	21(95.5%)	P=0.14
SD+PD	4(25%)	1(4.5%)	1

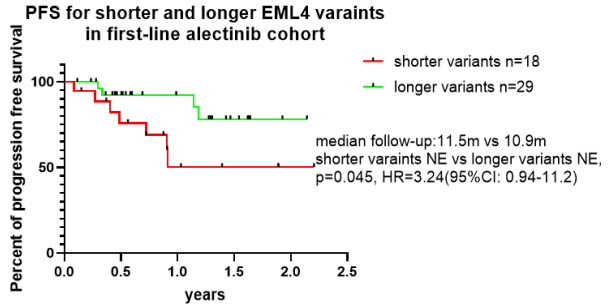
Table 2b:ORR between shorter and longer variants in patients with target lesions in first-line crizotinib cohort

	Shorter forms n=20	Longer forms n=24	P value
Radiological evaluation			
CR+PR	17(85%)	22(91.7%)	P=0.82
SD+PD	3(15%)	2(8.3%)	8

Figure 2a+2b:

PFS in Cohort 1 and Cohort 2 for different ALK variants

shorter variants were associated with significantly unfavorable PFS in Cohort 1



Higher frequency of ALK secondary mutation (64.7%(11/17) vs 38.5%(5/13), p=0.269) was reported in shorter forms

for patients who developed ALK secondary mutation, G1202R was much more common in shorter EML4 variants(90.9%(10/11) vs 0%(0/5), p=0.001)

Conclusion

Our study indicated that shorter and longer EML4-variants demonstrated different response to ALK inhibitors and resistance mechanism, therefore, more pertinent treatment strategy merits further exploration for different ALK variants