ALK-inhibitors in NSCLC: a tabulated review of randomised phase III trials

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Three inhibitors ALK-inhibitors have been assessed in six randomised phase III trials in patients with advanced anaplastic lymphoma kinase (ALK) positive Non Small-Cell Lung Cancer (NSCLC). Patient and tumour characteristics, efficacy, and safety results are summarised in *Tables 1, 2, and 3*, respectively.
Progression-free survival was the primary endpoint in all trials. In first-line, alectinib was superior to crizotonib, and both crizotinib and ceritinib were superior to pemetrexed plus platinum. Crizotinib and ceritinib were superior to pemetrexed or docetaxel in previously treated patients.
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The three tables can be found on the subsequent pages.

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TABLE 1. Patient and tumour characteristics.

	Previously untreated								Previously treated			
	J-ALEX		ALEX		PROFILE 1014		ASCEND-4		PROFILE 1007		ASCEND-5	
Treatment	Alectinib	Crizotinib	Crizotinib	Alectinib	Crizotinib	Chemo**	Ceritinib	Chemo**	Crizotinib	Chemo***	Ceritinib	Chemo***
Population												
N	**103**	**104**	**151**	**152**	**172**	**171**	**189**	**187**	**173**	**174**	**115**	**116**
Age (range)*	59.9 (25-84)	61.0 (27-85)	53.8 (18-91)	56.3 (25-88)	52 (22-76)	54 (19-78)	55 (22-81)	54 (22-80)	51 (22-81)	49 (24-85)	54 (44-63)	54 (47-64)
Male	40%	39%	42%	45%	40%	37%	46%	39%	43%	45%	41%	47%
Race												
Asian			46%	45%	45%	47%	40%	44%	46%	45%	26%	33%
ECOG performance												
0	52%	46%	93%	93%	94%	95%	37%	37%	42%	37%	49%	44%
1	46%	52%					57%	56%	49%	55%	43%	52
2	2%	2%	7%	7%	6%	5%	7%	6%	9%	8%	8%	4%
Cellular classification												
Adenocarcinoma	97%	99%	94%	90%	94%	94%	95%	98%	95%	94%	97%	97%
Squamous cell	2%	0%	1%	3%	6%	6%	5%	2%	3%	4%	0%	2%
Other	1%	1%	5%	7%							3%	1%
Stage												
IIIB	3%	3%	4%	4%	2%	2%	5%	3%	4%	4%	1%	1%
IV	74%	72%	96%	97%	98%	98%	95%	97%	95%	94%	99%	99%
recurrence	23%	25%										
Treatment line												
First	64%	64%	100%	100%	100%	100%	100%	100%				
Second	36%	36%							100%	100%	1%	
Third line											88%	88%
Fourth line											11%	12%
Prior crizotinib											100%	100%
Brain metastases	14%	28%	38%	42%	26%	27%	31%	33%	35%	34%	57%	59%
Smoking status												
Never	54%	59%	65%	61%	62%	65%	57%	65%	62%	64%	62%	53%
Current	2%	3%	3%	8%	6%	3%	8%	8%	3%	5%	3%	1%
Past smoker	44%	38%	32%	32%	33%	32%	35%	27%	34%	31%	34%	44%

*: median; **: pemetrexed 500 mg/m^2 plus either cisplatin 75 mg/m^2 or carboplatin AUC 5/6 every 3 weeks;
***: investigator's choice: pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 every 3 weeks

TABLE 2. Efficacy.

	Previously untreated								Previously treated			
	J-ALEX		ALEX		PROFILE 1014		ASCEND-4		PROFILE 1007		ASCEND-5	
Treatment	Alectinib	Crizotinib	Crizotinib	Alectinib	Crizotinib	Chemo	Ceritinib	Chemo	Crizotinib	Chemo	Ceritinib	Chemo
Efficacy												
Median follow up	22.0°°°	22.2°°°	17.6	18.6	17.4	16.7	19.7		12.2	12.1	16.5	
PFS IRC												
Median	25.9	10.2	11.1***	NE***	10.9	7.0	16.6	8.1	7.7	3.0	5.4	1.6
95 % CI	20.3-NE	8.3-12.0	9.1-13.1	17.7-NE	8.3-13.9	6.8-8.2	12.6-27.2	5.8-11.1	6.0-8.8	2.6-4.3	4.1-6.9	1.4-2.8
HR	0.38		0.47		0.45		0.55		0.49		0.49	
95 % CI	°°0.26-0.55		0.34-0.65		0.35-0.60		0.42-0.73		0.37-0.64		0.39-0.67	
p	< 0.0001		< 0.001		< 0.001		< 0.00001		< 0.001		< 0.001	
12-month	72%	40%	48.7%	68.4%								
95 % CI	29.1-50.8	61.9-82.6	40.4-56.9	70.0-75.9								
OS												
Median			NE	NE	NR	NR	NR	26.6	21.7°	21.9°	18.1	20.1
95 % CI			17.1-NE	19.9-NE			29.3-NE	22.8-NE	18.9-30.5	16.8-26.0	13.4-23.9	11.9-25.1
HR			0.76		0.82		0.73		0.85		1.00	
			0.48-1.2		0.54-1.26		0.5-1.08		0.66-1.10		0.67-1.49	
p			0.2405		0.1804		0.056		0.1145		0.496	
12-month			82.5%	82.3%	83.5%	78.7%			84%	67%		
95 % CI			76.0-88.9	78.4-90.2	76.7-88.5	71.3-84.2			77-89	59-73		
p			0.6789									
18-month					68.9	67.3						
95 % CI					59.5-76.1	58.1-74.9						
ORR IRC												
%	92%	79%	75.5%***	82.9%***	74%	45%	72.5%	26.7%	65%	20%	39.1%	6.9%
95% CI	85.6-97.5	70.5-87.3	67.8-82.1	76.0-88.5	67-81	37-53	65.5-78.7	20.3-33.7	58-72	14-26	30.2-48.7	3.0-13.1
p			0.09		< 0.001				<0.0001			
DOR												
Median	NE	11.2	11.1	NE	11.3	5.3	23.9	11.1	7.4	5.6	6.9	8.3
95 % CI	21.4-NE	8.4-21.4	7.9-13.0	NE-NE	8.1-13.8	4.1-5.8	16.6-NE	7.8-16.4	6.1-9.7	3.4-8.3	5.4-8.9	3.5-NE
HR	0.39		0.36									
95 % CI	0.24-0.63		0.24-0.53									
			< 0.0001									
Intracranial response												
%			25.9%	59.4%			72.7%	27.3%			35.3%	5.0%
95 % CI			12.3-39.0	46.4-71.5							14.2- 61.7	0.1-24.9
Duration of intracranial response												
Median			3.7	NE								
95 % CI			3.2-6.8	17.3-NE								
Intracranial benefit rate at 24 weeks					56%	25%	86.4%	50.0%	65%	20%		
95 % CI							65.1-97.1	28.2-71.8	58-72	14-26		
p					0.006				< 0.001			

°: Updated based on final OS analysis
°°: 99.7% CI
°°°: data from updated analysis submitted to EMA
***: systemic responses evaluated by investigator, CNS response evaluated by IRC; NR: not reported; NE: not evaluable

TABLE 3. Safety.

	Previously untreated								Previously treated			
	J-ALEX		ALEX		PROFILE 1014		ASCEND-4		PROFILE 1007		ASCEND-5	
Treatment	Alectinib	Crizotinib	Crizotinib	Alectinib	Crizotinib	Chemo	Ceritinib	Chemo	Crizotinib	Chemo	Ceritinib	Chemo
Safety												
Grade ≥ 3 adverse events												
Any	26%	52%	50%	41%			78%	62%			90%	81%
Diarrhoea	0%	2%	2%	0%	2%	1%	5%	1%	0%	1%	4%	1%
Nausea	0%	2%	3%	1%	1%	2%	3%	5%	1%	1%	8%	2%
Vomiting	0%	2%	3%	0%	2%	3%	5%	6%	1%	0%	8%	1%
ALT increased	1%	5%	15%	5%	14%	2%	31%	3%	16%	2%	21%	2%
AST increased	1%	13%	11%	5%			17%	2%			14%	1%
ALP increased								1%			6%	0%
γGT increased			1%	1%			7%	2%			21%	1%
Bilirubin increased	0%	0%	0%	2%								
Decreased appetite	1%	1%			2%	1%	1%	1%			2%	3%
Weight decreased							4%	1%			3%	1%
Weight increased			0%	1%								
Fatigue			0%	1%	3%	2%	4%	3%	2%	4%	5%	4%
Asthenia							3%	3%			5%	6%
Abdominal pain					0%	0%	2%	0%			1%	1%
Upper abdominal pain	0%	0%					2%	0%			1%	0%
Back pain	0%	0%					2%	2%			1%	3%
Blood creatinine increased	0%	0%					2%	0%			0%	0%
Constipation	1%	1%	0%		2%	0%	0%	0%	2%	0%	0%	0%
Headache	0%	0%			1%	0%	0%	1%			1%	2%
Pyrexia	1%	0%			0%	1%	0%	1%			2%	0%
Cough					0%	0%	0%	0%			0%	1%
Dyspnoea					3%	2%	2%	6%	4%	3%	3%	6%
Non-cardiac chest pain							1%	1%			1%	0%
Prolonged QTC	2%	7%	3%	0%					4%	0%	1%	0%
Rash	0%	1%							0%	0%	0%	0%
Arthralgia			1%	0%							0%	3%
Nasopharyngitis	0%	0%							0%	<1%	0%	0%
Alopecia			0%	0%					13%	19%	0%	0%
Neutropenia	2%	14%	4%	0%	11%	15%	1%	11%	0%	0%	1%	15%
Peripheral oedema	0%	1%	1%	0%	1%	1%						
Anaemia	1%	0%	1%	5%			2%	7%				
Serious adverse events	15%	26%	29%	28%	34%	28%					43%	32%
Adverse events requiring												
dose adjustments			21%	11%	6%	8%	80%	45%			80%	38%
dose interruption	29%	74%	25%	19%	41%	34%						
treatment discontinuation	9%	20%	13%	16%	12%	14%	5%	11%	17%	9%	5%	7%
Fatal adverse events	0%	0%	5%	3%	12%	2%	2%	0.6%	17%	4%	2%	0%
TR fatal adverse events	0%	0%	1%	0%	0%	0.6%	0%	0%	2%	1%	0%	0%

TR: treatment related