Real world outcome of crizotinib for positive ALK mutation:

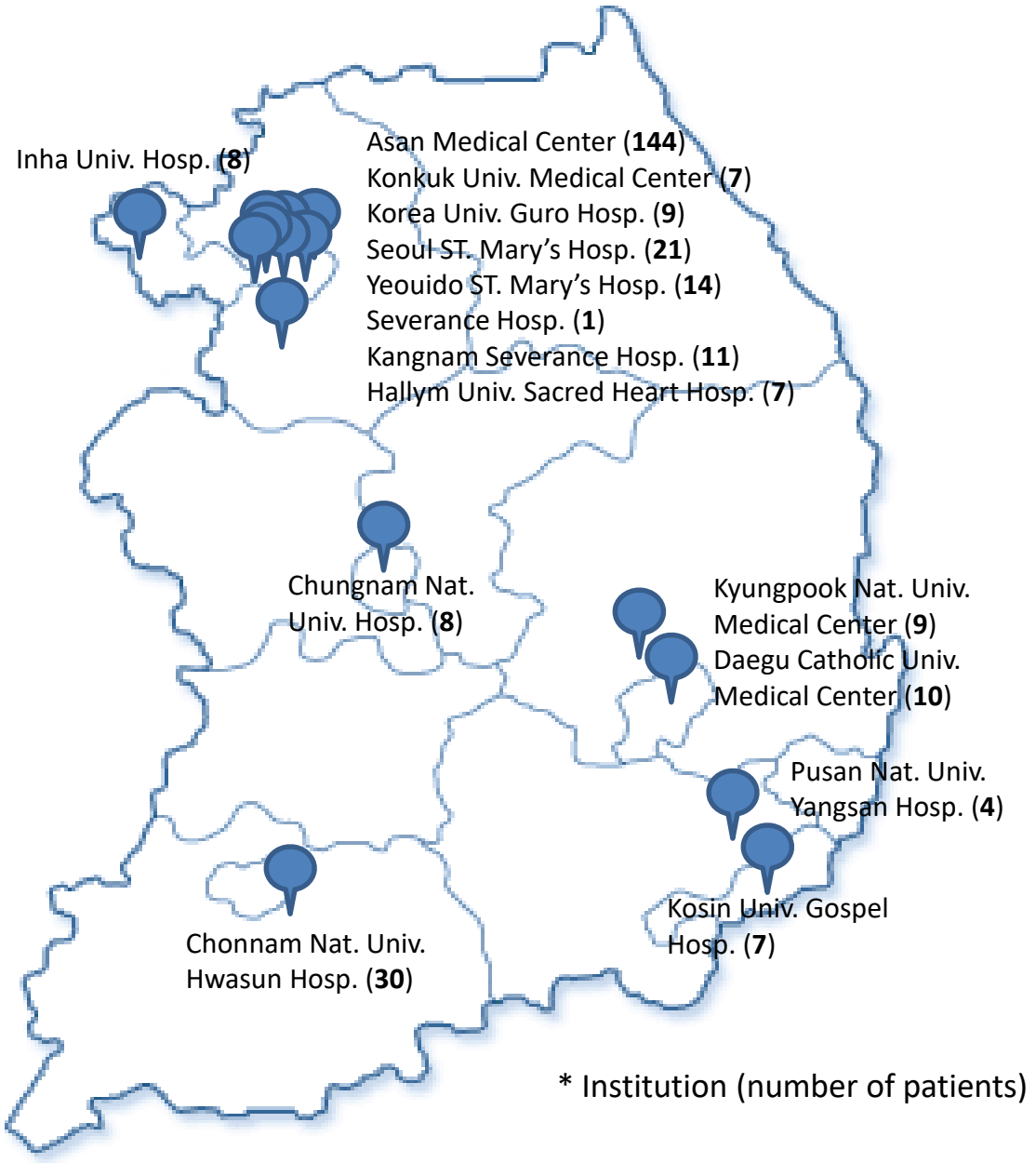
Multicenter retrospective cohort study in South Korea

Study aim

- Assessment of treatment patterns and outcomes of crizotinib in ALK+ NSCLC patients in tertiary hospitals of South Korea
- Investigating factors associated with PFS and OS after crizotinib initiation

METHODS

- 15 institutions: Total 290 patients
- Retrospective analysis of ALK+ NSCLC patients from 2009 ~ until date of IRB approval



RESULTS

Baseline characteristics	All patients (n = 290)	Setting of Crizotinib Initiation	
		First-Line (n = 113)	Second- or Later-Line (n = 177)
Age (years) at diagnosis [a]	57.0 (20-84)	62.0 (20-84)	55.0 (26-82)
Male	146 (50.3)	60 (53.1)	86 (48.6)
Smoking status at diagnosis [a]			
Current smoker	54 (18.6)	27 (23.9)	27 (15.3)
Former smoker	67 (23.1)	22 (19.5)	45 (25.4)
Never smoked	163 (56.2)	61 (54.0)	102 (57.6)
Unknown	6 (2.1)	3 (2.7)	3 (1.7)
Palliative reason			
Recurred	49 (16.9)	9 (8.0)	40 (22.6)
Initially advanced / metastatic	241 (83.1)	104 (92.0)	137 (77.4)

[a] : "At diagnosis" refers to at diagnosis of metastatic ALK+ NSCLC

	All patients (n = 290)	Setting of Crizotinib Initiation	
		First-Line (n = 113)	Second- or Later-Line (n = 177)
Histologic type			
Adenocarcinoma	280 (96.6)	108 (95.6)	172 (97.2)
Squamous cell carcinoma	3 (1.0)	1 (0.9)	2 (1.1)
Adenosquamous carcinoma	1 (0.3)	0 (0.0)	1 (0.6)
Sarcomatid carcinoma	1 (0.3)	0 (0.0)	1 (0.6)
NSCLC	3 (1.0)	3 (2.7)	0 (0.0)
Other	2 (0.7)	1 (0.9)	1 (0.6)
Mutation other than ALK			
EGFR (+)	8 (2.8)	1 (0.9)	7 (4.0)
KRAS (+)	2 (0.7)	0 (0.0)	2 (1.1)
Brain metastasis present [b]	66 (22.8)	37 (32.7)	29 (16.4)
No of metastatic organs ≥3	67 (23.1)	32 (28.3)	35 (19.8)

[b] : at/prior to crizotinib initiation

	All patients (n = 290)	Setting of Crizotinib Initiation	
		First-Line (n = 113)	Second- or Later-Line (n = 177)
Vital status at medical record abstraction			
Alive	140 (48.3)	48 (42.5)	92 (52.0)
Deceased	93 (32.0)	38 (33.6)	55 (31.1)
Transfer	31 (10.7)	13 (11.5)	18 (10.2)
Follow-up loss	26 (9.0)	14 (12.4)	13 (11.5)
Other cancer-directed Tx [c]			
Surgery	69 (23.8)	17 (15.0)	52 (29.4)
Radiotherapy	104 (35.9)	30 (26.5)	74 (41.8)
Duration (months) of observation	24.9 (21.4-28.4)	17.5 (14.3-20.7)	32.8 (28.0-37.6)

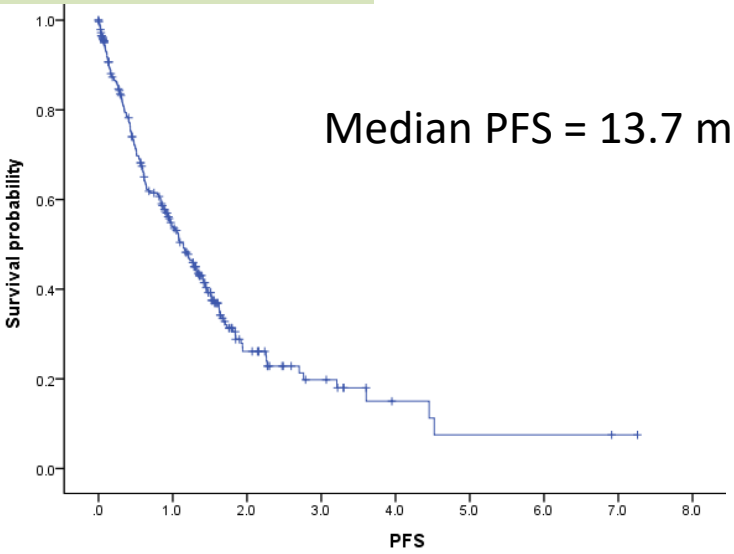
[c]: prior to crizotinib initiation

Efficacy of crizotinib

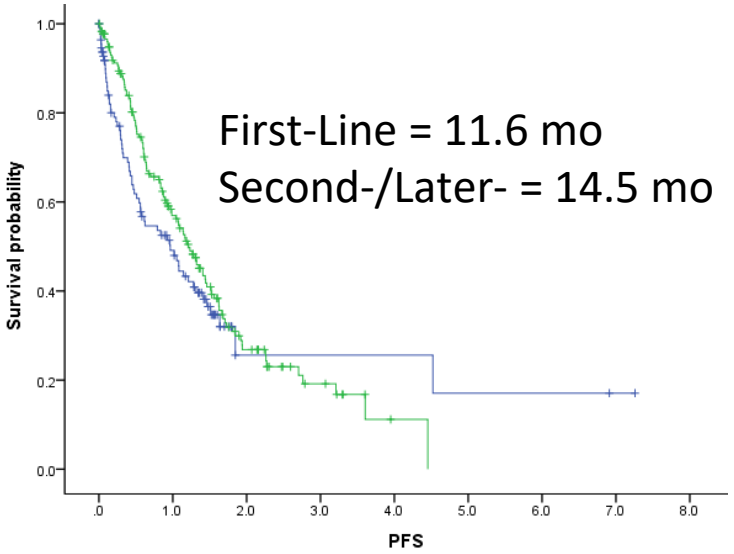
	All patients (n = 290)	Setting of Crizotinib Initiation	
		First-Line (n = 113)	Second- or Later-Line (n = 177)
Crizotinib response			
CR	3 (1.0)	1 (0.9)	2 (1.1)
PR	152 (52.4)	52 (46.0)	100 (56.5)
SD	84 (29.0)	30 (26.5)	54 (30.5)
PD	19 (6.6)	10 (8.8)	9 (5.1)
Not evaluable	32 (11.0)	20 (17.7)	12 (6.8)
ORR, %	60.1	57.0	61.8

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate

Estimates of PFS

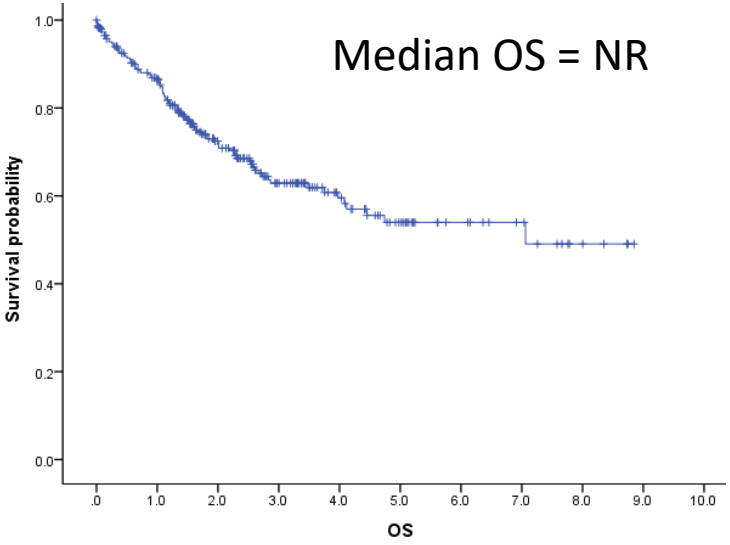


Median PFS = 13.7 mo

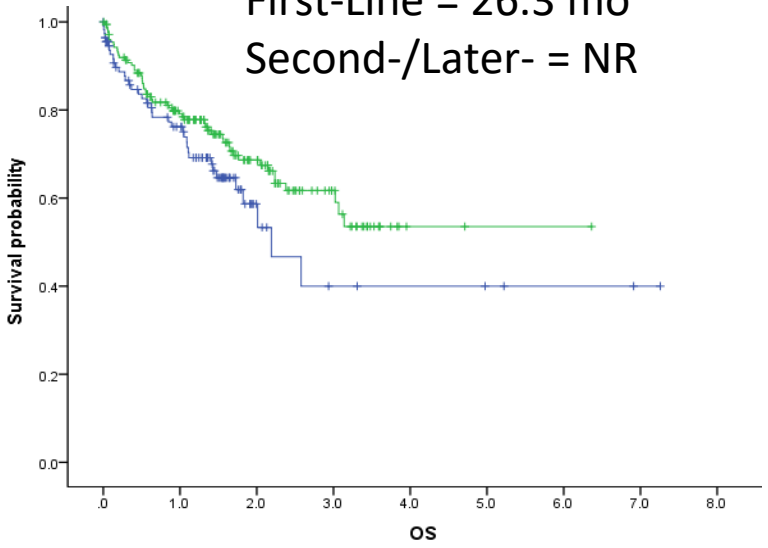


First-Line = 11.6 mo
Second-/Later- = 14.5 mo

Estimates of OS



Median OS = NR



First-Line = 26.3 mo
Second-/Later- = NR

Factors associated to PFS	Progression-free survival	
	Univariate HR (95% CI)	**Multivariate** HR (95% CI)
Age	1.016 (1.003-1.029)	1.020 (1.007-1.033)
Male	1.498 (1.128-1.988)	1.671 (1.112-2.512)
Smoking history		
Current smoker	1.824 (1.271-2.618)	
Ex-smoker	1.083 (0.758-1.548)	
Palliative reason		
Initially metastatic	2.244 (1.438-3.501)	2.106 (1.333-3.326)
No. of metastatic organs ≥ 3	2.385 (1.753-3.246)	2.124 (1.548-2.914)
Baseline brain metastasis	1.914 (1.400-2.615)	
Line of crizotinib		
Second- /later-line	0.816 (0.608-1.095)	
Response		
No response (SD+PD)	1.133 (0.836-1.536)	

Factors associated to OS

	Progression-free survival	
	Univariate	**Multivariate**
	HR (95% CI)	HR (95% CI)
Age	1.023 (1.005-1.041)	1.024 (1.007-1.042)
Male	1.624 (1.075-2.454)	1.769 (1.168-2.679)
Smoking history		
Current smoker	1.513 (0.890-2.574)	
Ex-smoker	1.150 (0.695-1.904)	
Palliative reason		
Initially metastatic	1.545 (1.075-2.221)	2.093 (0.998-4.389)
No. of metastatic organs ≥ 3	2.395 (1.571-3.652)	2.159 (1.402-3.323)
Baseline brain metastasis	1.693 (1.091-2.628)	
Line of crizotinib		
Second- /later-line	0.705 (0.463-1.071)	
Response		
No response (SD+PD)	1.087 (0.703-1.682)	

Tx patterns of crizotinib	All patients (n = 290)	Setting of Crizotinib Initiation	
		First-Line (n = 113)	Second- or Later-Line (n = 177)
Times (months) from initial diagnosis to crizotinib initiation			
Median (95% CI)	2.9 (1.6-4.2)	0.7 (0.6-0.8)	9.4 (7.2-11.6)
Duration (months) of crizotinib, Median (95% CI)	10.2 (7.6-12.9)	6.8 (4.9-8.6)	12.1 (9.7-14.6)
Last adjusted daily dose of crizotinib prescribed			
200 mg b.i.d.	22 (44.9)	7 (58.3)	15 (40.5)
250 mg b.i.d.	9 (18.4)	3 (25.0)	6 (16.2)
200 mg q.d.	3 (6.1)	0 (0.0)	3 (8.1)
250 mg q.d.	15 (30.6)	2 (16.7)	13 (35.1)
Crizotinib dose changes ≥ 1	49 (16.9)	12 (10.6)	37 (20.9)

	All patients (n = 290)	Setting of Crizotinib Initiation	
		First-Line (n = 113)	Second- or Later-Line (n = 177)
Adverse events	81 (27.9)	25 (22.1)	56 (31.6)
Nausea	9 (3.1)	2 (1.8)	7 (4.0)
Vomiting	13 (4.5)	3 (2.7)	10 (5.6)
Neutropenia	9 (3.1)	2 (1.8)	7 (4.0)
Hepatotoxicity	10 (3.4)	5 (4.4)	5 (2.8)
Heartburn	1 (0.3)	0 (0.0)	1 (0.6)
General malaise	1 (0.3)	0 (0.0)	1 (0.6)
Anorexia	5 (1.7)	1 (0.9)	4 (2.3)
Complicated kidney cyst	5 (1.7)	1 (0.9)	4 (2.3)
Leg edema	3 (1.0)	1 (0.9)	2 (1.1)
Pneumonitis	7 (2.4)	3 (2.7)	4 (2.3)
Pneumonia	6 (2.1)	1 (0.9)	5 (2.8)
Skin rash	3 (1.0)	2 (1.8)	1 (0.6)
Other intolerability	31 (10.7)	12 (10.6)	19 (10.7)

	All patients (n = 290)	Setting of Crizotinib Initiation	
		First-Line (n = 113)	Second- or Later-Line (n = 177)
Reason(s) for final discontinuation			
Ongoing crizotinib treatment	69 (23.8)	28 (24.8)	41 (23.2)
Disease progression	160 (55.2)	59 (52.2)	101 (57.1)
Treatment-related toxicity	18 (6.2)	6 (5.3)	12 (6.8)
Patient request	10 (3.4)	5 (2.8)	5 (4.4)
Follow-up loss	11 (3.8)	5 (2.8)	6 (5.3)
Transfer	15 (5.2)	7 (6.2)	8 (4.5)
Death	7 (2.4)	2 (1.8)	5 (2.8)

DISCUSSION

	All patients	Setting of Crizotinib Initiation	
		First-Line	Second- /Later-Line
ORR			
Current study	60.1%	57.0%	61.8%
Duruisseaux *et al*.	50.2%	51.1%	50.1%
Davis *et al*.	66.0%	69.0%	60.0%
Progression-free Survival			
Current study	13.7	11.6	14.6
Solomon *et al*. & Shaw *et al*.	-	10.9	7.7
Davis *et al*.	9.5	9.6	9.0
Duruisseaux *et al*.	-	-	6.8
Overall Survival			
Current study	NR	26.3	NR
Solomon *et al*. & Shaw *et al*.	NR/20.3	20.2	49.5/21.7
Davis *et al*.	23.4	23.4	NR
Duruisseaux *et al*.	16.6	-	-

DISCUSSION

- ORR generally consistent with previous reports
- PFS longer than previous studies
  - Different pharmacokinetic profiles of crizotinib between Asian/Non-Asian NSCLC patients
  - Lower body weight, body surface area → higher plasma concentration
  - Different ALK variant profile (V1, V3b)

J Tranl Med. 2016; 14: 296.
J Thorac Oncol. 2010;5(suppl. 5):S382.
Lancet Oncol. 2011;11:1004–1012.

DISCUSSION

- Prediction of PFS and OS after crizotinib initiation
  - SNU analysis of PROFILE 1004, 1007: Poor PS, No of meta≥3, No response to crizotinib associated with shorter PFS & OS

Korean J Intern Med. 2018.

DISCUSSION

- Limitation
  - Not all center included in South Korea → not generalizable
  - Response to crizotinib not checked in uniformed schedule → not directly comparable
  - Different follow-up period between 1st line and 2nd line users
- Strength and clinical implications
  - Real world population analysis of outcome of crizotinib