24P Efficacy and safety of 1st generation EGFR TKI retreatment in EGFR mutation positive/T790M negative patients who previously treated with 1st or 2nd generation EGFR TKI and cytotoxic chemotherapy.

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Introduction

- ✓ Although osimertinib has been approved for first-line therapy, 1st or 2nd generation EGFR TKIs are still being used as first-line therapy in more countries.
- ✓ Although T790M acquired resistance occurs 30 to 40% after the treatment of the first- or second-generation EGFR TKIs, most cases of T790M mutation-negative patients undergo cytotoxic chemotherapy or other supportive treatment.
- ✓ There are several reports that EGFR TKI re-administration may be helpful in T790M-negative patient. We did prospectively undergo EGFR TKIs retreatment trial as third line or later line therapy.

Objective

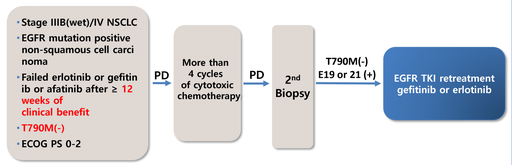
- ✓ We prospectively conducted the study on the effect of EGFR TKIs Retreatment as third or later line therapy in the patients who previously treated with 1st or 2nd generation EGFR TKI and cytotoxic chemotherapy.

Methods

- ✓ A total of 8 academic hospital sites participated in this clinical trial.
- ✓ The enrolled patients were resistant to 1st or 2nd generation EGFR-TKI as a 1st line treatment and then treated with chemotherapy for more than 4 cycles because of T790M-negative at 2nd biopsy.
- ✓ The enrolled patients had switched to a different first-generation EGFR-TKI (gefitinib 250mg or erlotinib 150mg) during subsequent retreatment.
- ✓ Primary endpoint : objective response rate,
- ✓ Secondary endpoints : progression free survival, overall survival, and safety

Study Design

Open label Phase II



Results

Table 1. Demographics and Baseline characteristics

Characteristics		N=63	%
Gender	F	37	58.7
	M	26	41.3
Smoking Hx	Never smoker	42	66.7
	Ex-smoker	19	30.1
	Current smoker	2	3.2
Baseline stage	III	2	3.2
	IV	61	96.8
Histologic type	Adenocarcinoma	62	98.4
	Adenosquamous carcinoma	1	1.6
Mutation type (Before retreatment)	E19 del	37	58.4
	L858R	25	40.0
	G719X	1	1.6
ECOG	0	13	20.6
	1	41	65.1
	2	9	14.3
Retreatment line	3	34	54.0
	4	21	33.2
	5	4	6.4
	6	3	4.8
	7	1	1.6

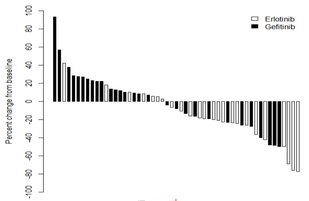
Table 2. The development rate of T790M after the retreatment of EGFR TKIs

Initial mutation type	T790M (-) n	T790M (-) %	T790M (+) n	T790M (+) %	T790M induction rate
E19 del	20	61	13	39	39%
L858R	17	77	5	23	23%
G719X	0		1	100	
L858R or L861Q	2		1	33	40%
UK	1		0	0	

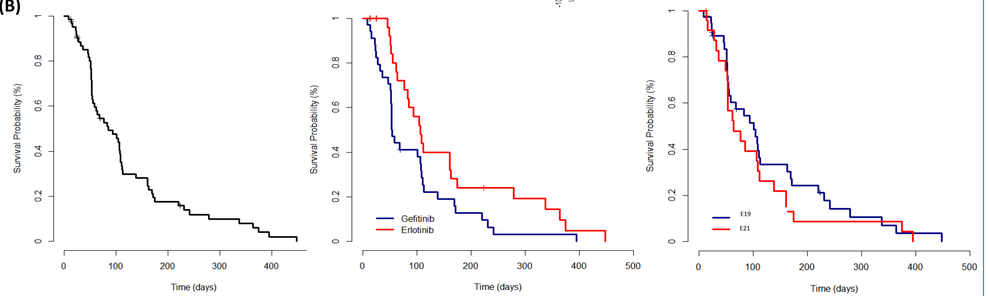
Efficacy

(A)

		All N=63	Gefitinib n=34	Erlotinib n=29	P-value
Best response	PR	9 14.3%	3 8.8%	6 20.7%	0.0858
	SD	23 36.5%	11 32.4%	12 41.4%	
	PD	23 36.5%	17 50%	6 20.7%	
	NE	8 12.7%	3 8.8%	5 17.2%	



(B)

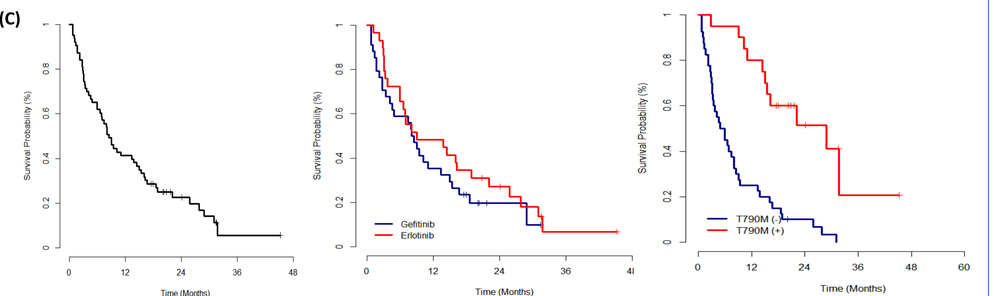


Total	Median (D)	95% CI	
63	85	54	108

retreament	Total	Median (D)	95% CI		P-value
Gefitinib	34	53.5	51	107	0.033
Erlotinib	29	106	77	163	

mutation	Total	Median (D)	95% CI		P-value
E19	37	101	54	113	0.375
E21	25	64	52	108	

(C)



Total	Median (M)	95% CI	
63	8.45	5.92	13.78

retreatment	Total	Median(M)	95% CI		P-value
Gefitinib	34	8.25	3.42	13.41	0.3236
erlotinib	29	9.01	5.92	18.87	

T790M	Total	Median (M)	95% CI		P-value
0	40	5.42	3.09	8.02	<0.001
1	20	28.93	14.5	NE	

Figure. 1. Investigators-assessed overall response and waterfall plot (A). Kaplan-Meier curves for PFS(B) and OS(C) of overall population, retreated EGFR TKIs and EGFR mutation types.

Safety

Table 3. Most common TRAEs in the overall population (n=63)

Treatment related AE (Any grade)	n	%
Blood and lymphatic system disorders	3	1.40
Cardiac disorders	1	0.47
Ear and labyrinth disorders	1	0.47
Eye disorders	2	0.93
Gastrointestinal disorders	59	27.57
General disorders and administration site conditions	17	7.94
Hepatobiliary disorders	1	0.47
Infections and infestations	10	4.67
Injury, poisoning and procedural complications	1	0.47
Metabolism and nutrition disorders	8	3.74
Musculoskeletal and connective tissue disorders	18	8.41
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	1.40
Nervous system disorders	6	2.80
Psychiatric disorders	5	2.34
Renal and urinary disorders	1	0.47
Respiratory, thoracic and mediastinal disorders	23	10.75
Skin and subcutaneous tissue disorders	41	19.16
Vascular disorders	1	0.47
Total	214	

Conclusion

Retreatment with EGFR-TKIs can be considered an option after the failure of cytotoxic chemotherapy for T790M(-) patients who were previously controlled by 1st or 2nd generation EGFR-TKI. The 1st generation EGFR TKIs retreatment may induce T790M mutation (33%) in patients who had not previously T790M mutation, leading to 3rd generation EGFR TKI sequential treatment and eventually prolongs OS.

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