The usefulness of liquid biopsy for ctDNA in patients with EGFR-mutant NSCLC during and after treatment with EGFR-TKIs

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Background 1

- Treatment with 1st or 2nd generation EGFR-TKIs is effective for NSCLC patients harboring EGFR mutation. However, acquired resistance is inevitable after a median period of 9 to 14 months.
- Although the resistance mechanisms vary, the most common one is T790M second mutation, which accounts for approximately 60% 1.
- Osimertinib, a 3rd generation EGFR-TKI targeting EGFR T790M mutation, is reported to be highly active against T790M positive NSCLC² and has been approved in Japan, as well as in the United States and Europe. Its efficacy is low in T790M-negative tumors which got acquired resistance to 1st or 2nd generation EGFR-TKIs.
- To detect T790M mutation following acquired resistance, re-biopsy of the tumor is necessary
- However, re-biopsy is often difficult and risky, depending on the size or location of the tumor. There is also a possibility of false-negative due to intra-tumor heterogeneity.

Background 2

- The optimal timing of treatment change remains elusive for an "effective" TKI. Many patients could receive benefit from "beyond-PD" TKI, and minor radiological worsening may not be the best time for histological exploration, including search for T790M. T790M may be evident, if ever, only after overt worsening (clinical PD) of the disease
- Frequent re-biopsies via invasive procedures (bronchoscopy or needle biopsy) are infeasible in the usual care of NSCLC patients. • Circulating tumor DNA (ctDNA) detected in the plasma sample is
- recognized as a noninvasive biomarker for quantifying the molecular analysis of NSCLC.
- Recently, Cobas EGFR Mutation Test[®] has been approved in Japan. using plasma specimens as a companion diagnostic test for the detection of EGFR mutations to identify such patients with NSCLC; however, its clinical utility in the trajectories of the patients is yet to be established.
- Cobas EGFR Mutation Test[®] is a noninvasive test, but its clinical data, including detection rate of T790M and the optimal timing of rebiopsy, are not sufficient.
- T790M monitoring in patients receiving Osimertinib by plasma ctDNA could give valuable clinical information.

Study design and purpose

Study Design

 Multicenter, prospective cohort study in Japan. • To investigate the diagnostic value of plasma ctDNA of EGFR mutations in the trajectory of patients with EGFR activating mutationpositive NSCLC treated with EGFR-TKIs, including Osimertinib.



Study design and purpose

Sample size justification

In the prior CSPOR-LC02 study (Observational study of treatment of EGFR mutation positive advanced or recurrent NSCLC: UMIN000010538), radiological PD was documented in approximately 80% of the patients. In the 80% of the patients who acquired resistance to gefitinib, about 60% patients are presumed to have T790M

From the above results, this study uses descriptive statistics, and it was set to 120 cases in consideration of feasibility of research.

Primary endpoint

- The plasma DNA T790M positivity rates by Cobas EGFR Mutation Test[®] in the T790M positive tumors patients.
- The plasma DNA T790M positivity rates by Cobas EGFR Mutation Test[®] at each clinical point.

Secondary endpoints

- The plasma DNA EGFR Exon 19 deletion or Exon 21 L858 mutation positivity rates by Cobas EGFR Mutation Test® in clinical courses.
- Time from plasma T790 positivity to tissue T790M positivity in the tissue T790M-nositive cases
- Response Rate and PFS with Osimertinib.
- Response Rate and PFS with re-challenge of other EGFR-TKIs.

Eligibility Criteria

Key inclusion criteria

- 1. Histologically confirmed advanced or postoperative recurrent NSCLC harbouring activating EGFR mutation.
- [Definitions of activating EGFR mutation] A) Exon 19 deletion (regardless of subtype)
- B) Exon 21 L858R
- C) Other rare mutations (e.g. Exon 18 G719X) * De novo T790M not excluded.
- 2. Being treated with an EGFR-TKI without disease progression, or, To be treated with an EGFR-TKI.
- 3. ECOG PS 0-2.
- Age ≥ 20 years
- 5. Signed informed consent

Key exclusion criteria

1. Prior therapy with an EGFR-TKI (other than the current therapy, if being treated with one)

Data Set

- Enrollment
- in Japan
- Enrollment: 122 patients
- Ineligible: 1 patient (prior EGFR-TKI therapy)
- · Eligible and assessable: 121 patients
- Collected CRF of 6 months after enrollment: 67 patients
- Not reached 6 months after enrollment: 54 patients
- Total 803 plasma samples between September 30, 2016, and September 12, 2017

Characteristics	No. of patients (n = 121)	%
Gender (Male/Female)	42/79	34.7/65.3
Age median (range)	72 (40-92)	
ECOG PS 0/1/2	64/54/3	52.9/44.6/2.5
Smoking history Never/Current/Past/ unknown	80/3/36/2	66.1/2.5/29.8/1.7
Clinical stage IIIA/IIIB/IV/Recurrence	1/3/78/39	
Recurrence Postoperative/irradiation /postoperative and radical irradiation	36/2/1	92.3/5.1/2.6
EGFR mutation		
Ex19 Del	61	50.4
Ex21 L858R	55	45.5
Other	5	4.1
T790M Denovo	0	0
EGFR samples		
Lung	93	76.9
Mediastinal Hilar lymph	6	5.0
Other lymph	3	2.5
Pleural effusion	15	12.4
Other	4	3.3

Patient characteristics

The Metastatic lesion before the therapy of EGFR-TKI			
Brain	33	15.5%	
Meningeal dissemination	2	0.9%	
Bone	32	15.0%	
Liver	8	3.8%	
adrenal gland	4	1.9%	
Lung	56	26.3%	
Pleural dissemination	32	15.0%	
Malignant pleural effusion	29	13.6%	
Pericardial effusion	2	0.9%	
Other	15	7.0%	
Total	213	100.0%	

History of treatment at enrollment

adiation irradiation site at er	nrollment	n	(%)
rain		10	55.6%
one		3	16.7%
hest (primary)		1	5.6%
hest(metastases)		1	5.6%
ther		0	0.0%
rain, bone		2	11.1%
one, others		1	5.6%
Total		18	100.0%
History of Cytotoxic agen	t	n	(%)
1 regimen		18	85.7%
2 regimens		2	9.5%
3 regimens		1	4.8%
Total		21	100.0%

1st EGFR-TKI at enrollment Status of EGFR-TKI at enrollment (%) Using before registration 103 85.1% Using after registration 18 14.9% Total 121 100.0% Treatment with 1st EGFR-TKI n (%) Gefitinib 50 41.3% Erlotinib 40 33.1% Afatinib 31 25.6%

Best overall tumor Response of st EGFR-TKI at enrollment	n	%
CR	10	9.7%
PR	71	68.9%
SD	12	11.7%
NE	10	9.7%
Total	103	100.0%

121

100.0%

Total

Consort diagrar	n
Enrollment (n=122) Eligible patients (n=121) plasma sampling (n=121) Collected CRF of 6 months after enrollment (n=57)	Ineligible 1 patient Because of Treatment history of two different EGR-R0s Total 803 plasma samples between september 30, 2016, and September 12, 2017
Continuation of 1 st EGFR-TKI (n=48) End of Post treatment after the 1 st EGFR-TKI (n=13)	1 st EGFR-TKI (n=19) none (n=6)
Osimertinib (n=4) Other treatment (n=9)

		R
Best overall tumor Response of 1 st EGFR-TKI	n	%
CR	8	11.9%
PR	39	58.2%
SD	10	14.9%
PD	8	11.9%
NE	2	3.0%
Total	67	100.0%
Treatment status of 6 months after enrollment	n	%
Continuation of 1 st EGFR-TKI	48	71.6%
End of 1 st EGFR-TKI	19	28.4%
Total	67	100.0%
Post treatment after the 1 st EGFR-TKI	n	%
Osimertinib	4	21.1%
EGFR-TKI (other Osimertinib)	3	15.8%
EGFR-TKI+Bevacizumab	1	5.3%
Platinum regimen	5	26.3%
None	6	31.5%
Total	19	100.0%
	-	
1 st Re-biopsy (histological samples)	n	%
Yes	10	14.9%
No	57	85.1%
Total	67	100.0%
The lesion of ^{1st} Re-biopsy (histological samples)	n	%
Lung	6	60.0%
Mediastinal Hilar lymph	1	10.0%
Pleural effusion	2	20.0%
Other	1	10.0%
Total	10	100.0%
Detection of EGFR mutation		~
by 1 st Re-biopsy (histological samples)	n	%
Positive	-	
Only common mt	4	40.0%
Common mt+T790M [*]	2	20.0%
Negative Total	4	40.0%
<u>X No detection of</u> he treatment after detection of T790M		
y histological samples	Ν	%
Osimertinib	1	50.0%
Bevond PD	1	50.0%

Total

2

100.0%

Best overall tumor Response of 1 st EGFR-TKI	n	%
CR	8	11.9%
PR	39	58.2%
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itive		
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Common mt+T790M [*]	2	20.0%
gative	4	40.0%
Total	10	100.0%
X No detection of	f T790 in pla	isma samples
treatment after detection of T790M istological samples	N	%
Osimertinib	1	50.0%
Beyond PD	1	50.0%

Best overall tumor Response of 1 st EGFR-TKI	n	%
CR	8	11.9%
PR	39	58.2%
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Post treatment after the 1 st EGFR-TKI	n	%
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Other	1	10.0%
Total	10	100.0%
Detection of EGFR mutation	n	%
by 1 st Re-biopsy (histological samples)		
Positive	4	40.0%
Only common mt Common mt+T790M [※]	4	40.0% 20.0%
Negative	4	40.0%
Total	10	100.0%
X No detection of		
he treatment after detection of T790M y histological samples	N	%
Osimertinib	1	50.0%
Beyond PD	1	50.0%

1* EGFR-TKI R 31 CR 8 11.9% PR 39 58.2% SD 10 14.9% PD 8 11.9% NE 2 3.0% Total 67 100.0% Treatment status of 6 months after enrollment n % Continuation of 1st EGFR-TKI 48 71.6% End of 1st EGFR-TKI 19 28.4% Total 67 100.0% Post treatment after the 1st EGFR-TKI n % Continuation of 1st EGFR-TKI n % Osimertinib 4 21.1% EGFR-TKI (other Osimertinib) 3 15.8% EGFR-TKI (other Osimertinib) 3 15.8% Platinum regimen 5 26.3% None 6 31.5% Total 19 100.0% Yes 10 14.9% No 57 85.1% Total 6 60.0% <td< th=""><th>Best overall tumor Response of</th><th>n</th><th>%</th></td<>	Best overall tumor Response of	n	%
PR 39 58.2% SD 10 14.9% PD 8 11.9% NE 2 3.0% Total 67 100.0% Treatment status of 6 months after enrollment n % Continuation of 1 st EGFR-TKI 48 71.6% End of 1 st EGFR-TKI 19 28.4% Total 67 100.0% Post treatment after the 1 st EGFR-TKI n % Continuation of 1 st EGFR-TKI n % Post treatment after the 1 st EGFR-TKI n % Cosimertinib 4 21.1% EGFR-TKI (other Osimertinib) 3 15.8% EGFR-TKI Bevacizumab 1 5.3% Platinum regimen 5 26.3% None 6 31.5% Ital 10 10.0% Yes 10 14.9% No 57 85.1% Ital 6 60.0% Mediastinal Hilar lymph 1	1 st EGFR-TKI	"	
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Post treatment after the 1st EGFR-TKI n % Osimertinib 4 21.1% EGFR-TKI (other Osimertinib) 3 15.8% EGFR-TKI +Bevacizumab 1 5.3% Platinum regimen 5 26.3% None 6 31.5% Total 19 100.0% 1st Re-biopsy (histological samples) n % Yes 10 14.9% No 57 85.1% Total 6 60.0% Mediastinal Hilar kymph 1 10.0% Pleural effusion 2 20.0% Other 1 10.0% Total 10 100.0% Pleural effusion 2 20.0% Other 1 10.0% Positive 4 40.0% Common mt 4 40.0% 4 Common mt rT790M ^{3%} 2 20.0% 10 Negative 4 40.0.0% 3 10 <tr< td=""><td>End of 1st EGFR-TKI</td><td>19</td><td>28.4%</td></tr<>	End of 1 st EGFR-TKI	19	28.4%
Osimertinib421.1%EGFR-TKI (other Osimertinib)315.8%EGFR-TKI+Bevacizumab15.3%Platinum regimen526.3%None631.5%Total19100.0%Total19100.0%Yes101st Re-biopsy (histological samples)nNo5785.1%Total67100.0%The lesion of 1st Re-biopsy (histological samples)n%%66.0%Mediastinal Hilar lymph110.0%Pleural effusion220.0%Other110.0%Total10100.0%Common mt+T790M ³⁶ 220.0%Negative440.0%Total10100.0%Xivo detection of T790M1100.0%Wistological samples%%No57%Sivo detection of T790M150.0%	Total	67	100.0%
EGFR-TKI (other Osimertinib)315.8%EGFR-TKI+Bevacizumab15.3%Platinum regimen526.3%None631.5%Total19100.0%Total19100.0%1st Re-biopsy (histological samples)n%Yes1014.9%No5785.1%Total67100.0%The lesion of 1st Re-biopsy (histological samples)n%Mediastinal Hilar lymph110.0%Pleural effusion220.0%Other10100.0%Total10100.0%Positiven%Only common mt Common mt+T790M ³⁶ 440.0%Negative440.0%Total10100.0%Xest No detection of T790M by histological samples%The treatment after detection of T790M by histological samples%	Post treatment after the 1 st EGFR-TKI	n	%
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Platinum regimen 5 26.3% None 6 31.5% Total 19 100.0% 1st Re-biopsy (histological samples) n % Yes 10 14.9% No 57 85.1% Total 67 100.0% The lesion of ^{1st} Re-biopsy (histological samples) n % Lung 6 60.0% Mediastinal Hilar lymph 1 10.0% Pleural effusion 2 20.0% Other 1 10.0% Total 10 100.0% Positive N % Only common mt 4 40.0% Common mt+T790M ^{3%} 2 20.0% Negative 4 40.0% Total 10 100.0% Xex No detection of T790M MS 2 20.0% Negative 4 40.0% 4 Osimertinib 10 100.0% 3	EGFR-TKI (other Osimertinib)	3	15.8%
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Total 19 100.0% Total 19 100.0% 1st Re-biopsy (histological samples) n % Yes 10 14.9% No 57 85.1% Total 67 100.0% Total 67 100.0% The lesion of ^{1st} Re-biopsy (histological samples) n % Lung 6 60.0% Mediastinal Hilar lymph 1 10.0% Pleural effusion 2 20.0% Other 1 10.0% Detection of EGFR mutation by 1st Re-biopsy (histological samples) n % Positive 4 40.0% Common mt+T790M ^{XE} 2 20.0% Negative 4 40.0% Xotal 10 100.0% Xextor 10 100.0% Xotal 4 40.0% Common mt+T790M ^{XE} 2 20.0% Xotal 10 100.0% Xotal 10 100.0%	Platinum regimen	5	26.3%
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Yes 10 14.9% No 57 85.1% Total 67 100.0% The lesion of ^{1st} Re-biopsy (histological samples) n % Lung 6 60.0% Mediastinal Hilar lymph 1 10.0% Pleural effusion 2 20.0% Other 1 10.0% Total 10 100.0% Other 1 10.0% Other 1 0.0% Other 10 100.0% Common mt 2 20.0% Only common mt 4 40.0% Common mt+T790M ^{XE} 2 20.0% Negative 4 40.0% Total 10 100.0% X No detection of T790 in plasma samples X Motiological samples N % Osimertinib 1 50.0%	Total	19	100.0%
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The lesion of ^{1st} Re-biopsy (histological samples) n % Lung 6 60.0% Mediastinal Hilar lymph 1 10.0% Pleural effusion 2 20.0% Other 1 10.0% Total 10 100.0% Detection of EGFR mutation by 1st Re-biopsy (histological samples) n % Positive Only common mt Common mt+T790M [※] 2 20.0% Negative 4 40.0% Total 10 100.0% X No detection of T790 in plasma samples % The treatment after detection of T790M by histological samples N %	No	57	85.1%
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(histological samples) Lung 6 60.0% Mediastinal Hilar lymph 1 10.0% Pleural effusion 2 20.0% Other 1 10.0% Total 10 100.0% Detection of EGFR mutation by 1st Re-biopsy (histological samples) Positive n % Common mt 4 40.0% Common mt+T790M ^{3%} 2 20.0% Negative 4 40.0% Total 10 100.0% X No detection of T790 in plasma samples % The treatment after detection of T790M by histological samples % Osimertinib 1 50.0%	The lesion of ^{1st} Re-biopsy		0/
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Pleural effusion 2 20.0% Other 1 10.0% Total 10 100.0% Detection of EGFR mutation by 1st Re-biopsy (histological samples) n % Positive Only common mt Common mt+T790M [%] 2 20.0% Negative 4 40.0% Total 10 100.0% X No detection of T790 in plasma samples % The treatment after detection of T790M by histological samples N % Osimertinib 1 50.0%	Lung	6	60.0%
Other 1 10.0% Total 10 100.0% Detection of EGFR mutation by 1st Re-biopsy (histological samples) n % Positive Only common mt Common mt+T790M [®] 2 20.0% Negative 4 40.0% Total 10 100.0% Ko detection of T790 in plasma samples % % The treatment after detection of T790M by histological samples N % Osimertinib 1 50.0% %	Mediastinal Hilar lymph	1	10.0%
Total 10 100.0% Detection of EGFR mutation by 1st Re-biopsy (histological samples) n % Positive Only common mt Common mt+T790M [®] 4 40.0% Negative 4 40.0% Total 10 100.0% X No detection of T790 in plasma samples % The treatment after detection of T790M by histological samples N % Osimertinib 1 50.0%	Pleural effusion	2	20.0%
Detection of EGFR mutation by 1st Re-biopsy (histological samples) n % Positive Only common mt Common mt+T790M [®] 4 40.0% Negative 4 40.0% Total 10 100.0% <u>X</u> No detection of T790 in plasma samples % The treatment after detection of T790M by histological samples N % Osimertinib 1 50.0%	Other	1	10.0%
by 1st Re-biopsy (histological samples) n % Positive Only common mt Common mt+T790M [%] 4 40.0% Negative 4 40.0% Total 10 100.0% X No detection of T790 in plasma samples X % The treatment after detection of T790M N % Osimertinib 1 50.0%	Total	10	100.0%
by 1st Re-biopsy (histological samples) n % Positive Only common mt Common mt+T790M [%] 4 40.0% Negative 4 40.0% Total 10 100.0% X No detection of T790 in plasma samples X % The treatment after detection of T790M N % Osimertinib 1 50.0%			
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Negative 4 40.0% Total 10 100.0% XNo detection of T790 in plasma samples 10 100.0% The treatment after detection of T790M by histological samples N % Osimertinib 1 50.0%	·		40.0%
Total 10 100.0% X No detection of T790 in plasma samples The treatment after detection of T790M N % by histological samples Osimertinib 1 50.0%			20.0%
X No detection of T790 in plasma samples The treatment after detection of T790M N % by histological samples 0simertinib 1 50.0%	•		40.0%
The treatment after detection of T790M N % by histological samples 0 50.0%	Total	10	100.0%
by histological samples N % Osimertinib 1 50.0%	X No detection of	f T790 in pla	asma samples
Osimertinib 1 50.0%	The treatment after detection of T790M by histological samples	Ν	%
Beyond PD 1 50.0%		1	50.0%
	Beyond PD	1	50.0%

- Between September 30, 2016, and March 10, 2017, at 15 centres

- Data cut-off for this analysis: August 31, 2017



UMIN#000023248

sults

Detection of T790M after 1 st EGFR-TKI treatment by plasma samples	n	%
Positive	11**	9.1%
Negative	110	90.9%
Total	120	100.0%
X No detection of T79	0 by histolog	tical camples

※ No detection of T790 by histological sample

The treatment after Detection of T790M by plasma samples	n	%
Osimertinib	3	27.3%
Beyond PD	2	18.2%
unknown	6	54.5%
Total	11	100.0%

Conclusions

- In this multi-institutional study, periodic monitoring of ctDNA for EGFR mutation, including T790M, was feasible, with 121 patients. So far, 803 plasma specimens were collected in 11 months for analysis of EGFR gene mutations.
- So far, 19 patients got acquired resistance to the initial EGFR-TKI. Of those, ctDNA revealed T790M in 11 patients, whereas histological re-biopsy revealed T790M in 2 patients.
- Follow-up of the patients and accumulation of the data would reveal value of T790M ctDNA monitoring in EGFR-TKI-treated patients, including those receiving osimertinib.

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