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The plasma ctDNA monitoring during epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment in patients with EGFR mutant non-small cell lung cancer (JP-CLEAR trial)

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Comprehensive Support Project

Abstract

Background: Approximately 60% of EGFR mutant non-small cell lung cancer (NSCLC) patients treated with first/second generation EGFR-TKIs will acquire resistance by the T790M mutation. Since osimertinib, a third generation EGFR-TKI, is active for NSCLC with T790M, re-biopsy to examine the T790M status at the disease progression is necessary to administer osimertinib adequately. T790M monitoring in patients receiving EGFR-TKIs by plasma ctDNA could give valuable clinical information.

Methods: Patients with advanced or post-operative recurrent NSCLC with the sensitive EGFR mutations who receive the first EGFR-TKI treatment are eligible. Plasma samples at the baseline and the several timings of the disease are analyzed for EGFR mutation status using Cobas EGFR Mutation Test®.

Results: Between September 2016 and March 2017, 122 patients at 15 institutions in Japan were enrolled. Total 1291 plasma samples from 121 patients were analyzed for EGFR mutation status at Aug 2018. At the baseline, the sensitive EGFR mutation (Ex19 del 14, L858R 15) was detected in 29 (23.9%) of 121 patients and the resistant EGFR mutation T790M was detected in 3 (2.5%) patients. During the follow up period, 66 (54.5%) patients experienced disease progression and 64 (52.9%) stopped the first EGFR-TKI treatment. Twenty-two (18.2%) patients showed T790M in plasma ctDNA. Median time from the first EGFR-TKI treatment to the detection of T790M in plasma ctDNA was 441 days. Although 33 patients received re-biopsy to examine the EGFR mutation status at the disease progression, T790M was detected in only nine (22.0%) of the 41 re-biopsied materials. Seven (77.8%) of the nine patients who showed T790M in the re-biopsied materials received osimertinib, whereas 15 (68.2%) of the 22 patients with T790M detection in plasma received osimertinib, 3 (13.6%) continued the first EGFR-TKI, and 2 (9.0%) received platinum-based chemotherapy.

Conclusions: Although ctDNA monitoring during the EGFR-TKI treatment is useful, further investigation is necessary to elucidate the efficacy of osimertinib treatment based on the T790M detection in plasma ctDNA.

Clinical Trial Number: UMIN 000023248

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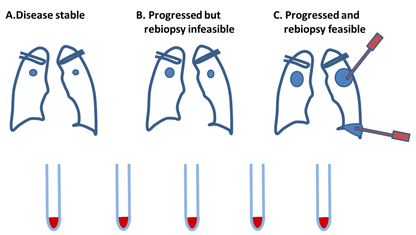
Circulating ctDNA monitoring



Circulating ctDNA monitoring : less invasive and repeated monitoring possible.

Introduction

- Treatment with 1st or 2nd generation epidermal growth factor receptor-tyrosine kinase inhibitors(EGFR-TKIs) is effective for non-small cell lung cancer(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%.
- Osimertinib, a 3rd generation EGFR-TKI targeting EGFR T790M mutation, is reported to be highly active against T790M positive NSCLC.
- To detect T790M mutation following acquired resistance, re-biopsy of the tumor is necessary. However, frequent re-biopsies with invasive procedures (bronchoscopy or needle biopsy) are infeasible in the usual care of NSCLC patients. There is also a possibility of false-negative due to intra-tumor heterogeneiety.
- Circulating tumor DNA (ctDNA) detected in the plasma sample is recognized as a noninvasive biomarker for quantifying the molecular analysis of NSCLC.
- Cobas EGFR Mutation Test® using plasma specimens as a companion diagnostic test for the detection of EGFR mutations has been approved to identify such patients with NSCLC.
- T790M monitoring in patients receiving oimertinib by plasma ctDNA could give valuable clinical information.

Study Objectives

Primary endpoints

- 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 L858R mutation positivity rates by Cobas EGFR Mutation Test® in clinical courses.
- Time from plasma T790M positivity to tissue T790M positivity in the tissue T790M-positive cases.
- Response Rate and PFS with osimertinib.
- Response Rate and PFS with re-challenge of other EGFR-TKIs.

Patients and methods

Key inclusion criteria

Histologically confirmed advanced or postoperative recurrent NSCLC harboring 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.

Key exclusion criteria

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

Plasma sampling schedule

- All patients: Baseline and every 1~3 month, until end of treatment with EGFR-TKI or second biopsy of the lesion of PD revealed no T790M mutation.
- All patients: At the time of radiological PD to EGFR-TKI.
- Those who continued to receive 1st treatment of EGFR-TKI beyond radiological PD: At the time of systemic PD, and/or symptomatic PD.
- Those who received second biopsy for PD: At the time of the second biopsy.
- Those who received osimertinib: Immediately before osimertinib administration.
- Those who received another EGFR-TKI than osimertinib as re-challenge:Immediately before re-challenge administration.

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.

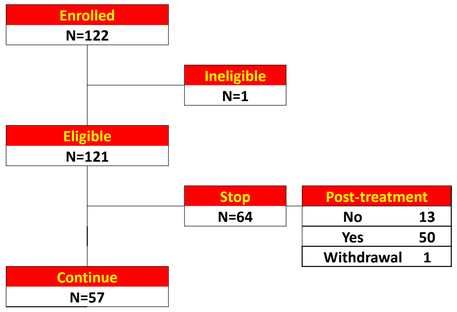
Results

122 patients were enrolled between Sep 2016 and Mar 2017 from 15 centers in Japan. Of them, 121 patients were eligible and assessable. At data cut-off for this analysis, Aug 30, 2018, CRF of 6 and 12 months after enrollment were collected from 121 and 109 patients, respectively.
Median follow up time was 364 days(SD 93.8).
Total 1291 plasma samples were analyzed.

Patient characteristics

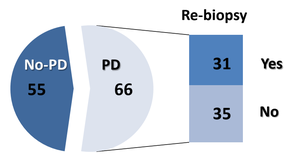
		N=121	
Age	Median(range)	72	(40-92)
Gender	Male	42	34.7%
	Female	79	65.0%
PS	0	64	52.9%
	1	54	44.6%
	2	3	2.5%
Smoking status	Never	80	66.1%
	Current/Former	39	32.3%
	Unknown	2	1.7%
Histology	Adenocarcinoma	118	97.5%
	Others	3	2.5%
EGFR genotype	Ex 19 del	61	50.4%
	Ex 21 L858R	55	45.5%
	Others	4	3.36%
	Ex 21 L858R + other	1	0.8%
Stage	IIIA	1	0.8%
	IIIB	3	2.5%
	IV	78	64.5%
	recurrence	39	32.2%
EGFR-TKI	Gefitinib	50	41.3%
	Erlotinib	40	33.1%
	Afatinib	31	25.6%

Consort diagram

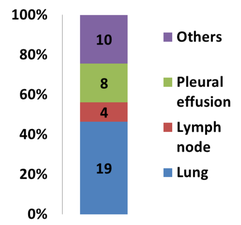


EGFR mutation status of rebiopsied samples

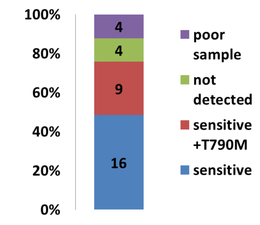
A. Frequency of rebiopsy



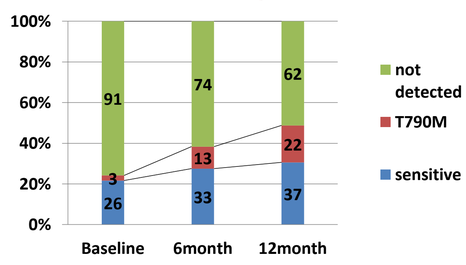
B. Samples rebiopsied



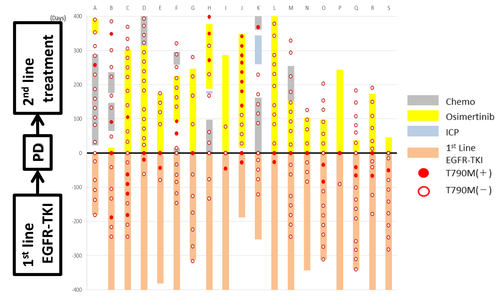
C. EGFR status of rebiopsied sample



EGFR mutation status of plasma ctDNA



Timing of T790M detection in plasma ctDNA



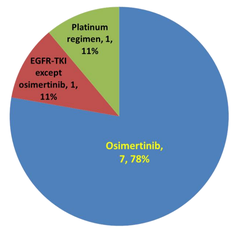
In 15(78.9%) of 19 patients with T790M detection in plasma, T790M was detected in plasma before and/or at disease progression(PD).

Treatment after failure of the first EGFR-TKI

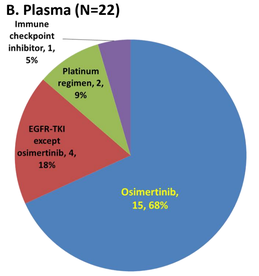
	2nd	3rd	4th
Osimertinib	20	2	1
EGFR-TKI except osimertinib	10	2	1
EGFR-TKI+Bevacizumab	1	0	0
Platinum regimen	16	4	0
Non-platinum regimen	3	4	2
Immune checkpoint inhibitor	0	3	1

Treatment after T790M detection

A. Re-biopsied (N=9)



B. Plasma (N=22)



Conclusions

Although ctDNA monitoring during the EGFR-TKI treatment is useful, further investigation is necessary to elucidate the efficacy of osimertinib treatment based on the T790M detection in plasma ctDNA.

Acknowledgments

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