P2.09-23. A Multicentre, Real-World Observational Study of First-Line Osimertinib and Post Progression Patterns in EGFR Positive NSCLC (Reiwa Study)

K. Watanabe[1], Y. Hosomi[1], K. Naoki[2], T. Kato[3], Y. Tsukita[4], H. Matsumoto[5], K. Yoh[6], Y. Fujisaka[7], S. Takahashi[8], S. Takata[9], K. Usui[10], K. Kishi[11], G. Naka[12], S. Tamano[13], K. Uemura[14], H. Kunitoh[15]

[1]Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo/JP ,[2]Kitasato University School of Medicine, Sagamihara/JP ,[3]Kanagawa Cancer Center, Yokohama/JP ,[4]Tohoku University Graduate School of Medicine, Sendai/JP ,[5]Hyogo Prefectural Amagasaki General Medical Center, Amagasaki/JP ,[6]National Cancer Center Hospital East, Kashiwa/JP ,[7]Osaka Medical and Pharmaceutical University Hospital, Takatsuki/JP ,[8]Tokyo Medical University, Tokyo/JP ,[9]Kyorin University School of Medicine, Mitaka/JP ,[10]NTT Medical Center Tokyo, Tokyo/JP ,[11]Toho University Omori Medical Center, Tokyo/JP ,[12]National Center for Global Health and Medicine, Tokyo/JP ,[13]Graduate School of Interdisciplinary Information Studies, The University of Tokyo, Tokyo/JP ,[14]The Interfaculty Initiative in Information Studies, The University of Tokyo, Tokyo/JP ,[15]Japan Red Cross Medical Center, Tokyo/JP

Comprehensive Support Project

Declaration of interests

This study was sponsored by the Public Health Research Foundation.

This study is financially supported by AstraZeneca.

AstraZeneca is not be directly involved in the data management, source data verification, or the statistical analysis.

Background

- Osimertinib is a third-generation, irreversible epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR-T790M (resistant) mutations.

- In a phase III trial (FLAURA), osimertinib showed efficacy superior to that of first-generation gefitinib and erlotinib, with a similar safety profile and lower rates of serious adverse events.

- Osimertinib is widely used as the first-line treatment for EGFR mutation-positive non-small cell lung cancer (NSCLC) , but its efficacy and safety of osimertinib in real-world clinical practice remain to be fully elucidated in Japanese population.

- In addition, most cases ultimately acquire resistance to osimertinib, and no effective treatment has been currently established for cases having progressive disease (PD) with osimertinib.

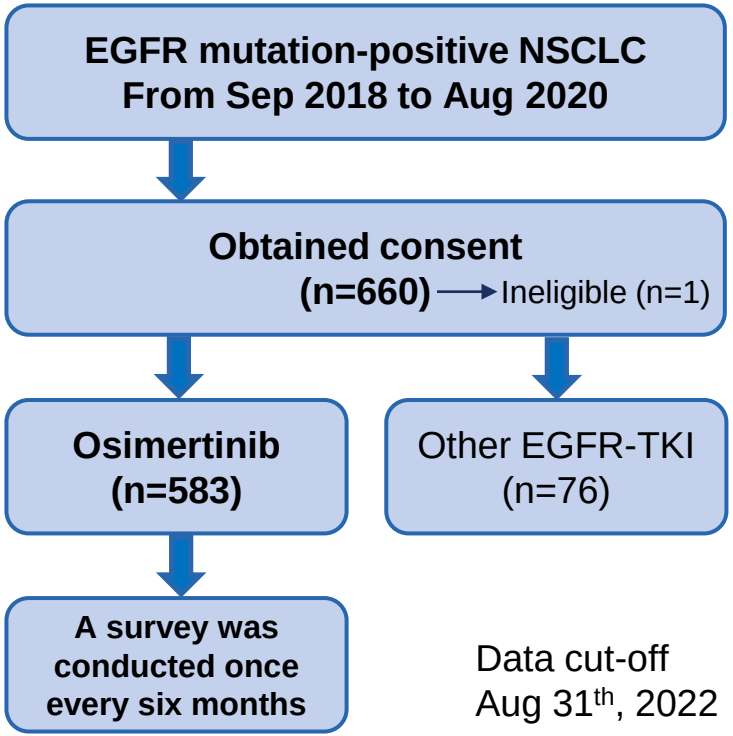
Methods

【Design】

A multicenter, prospective real-world cohort study

【Patients】

- EGFR mutation-positive
- Advanced or recurrent NSCLC patients
- Started EGFR-TKI treatment from September 2018 to August 2020 were enrolled
- Those receiving first-line osimertinib monotherapy were followed-up for efficacy, safety, progression patterns, post-progression treatments and outcomes until August 2022.



Methods

【 Primary endpoint 】

- Progression free survival* with Osimertinib

* Time from the start of osimertinib to RECIST PD or death from any cause.

- Percentage of patients with progression patterns when RECIST PD was encountered with osimertinib treatment.

Patient characteristics (n=583)

	Median (range) or number (%)
Age, median (range), years	72 (30-95)
Gender, male / female	224 (38.4) / 359 (61.6)
ECOG PS*, 0 / 1 / 2 / 3 / 4 / missing	216 (37.1) / 281 (48.2) / 60 (10.3) / 20 (3.4) / 2 (0.3) / 4 (0.7%)
Smoking status, never / former / current	325 (55.8) / 224 (38.4) / 34 (5.8)
Histology, adeno / squamous / NOS / LCNEC	571 (97.9) / 9 (1.5) / 2 (0.3) / 1 (0.1)
Mutation type*, Ex19del / L858R / others	285 (48.9) / 266 (45.6) / 33 (5.7)
Stage, locally advanced / metastatic / recurrence	19 (3.3) / 395 (67.8) / 169 (29.0)
Brain metastases, yes / no	169 (29.0) / 414 (71.0)

NOS: not otherwise specified, LCNEC: large cell neuroendocrine carcinoma.
* One patient had both Ex19del and L858R mutations.

Follow-up period, median 28.5 months (range, 0.1-48.0)

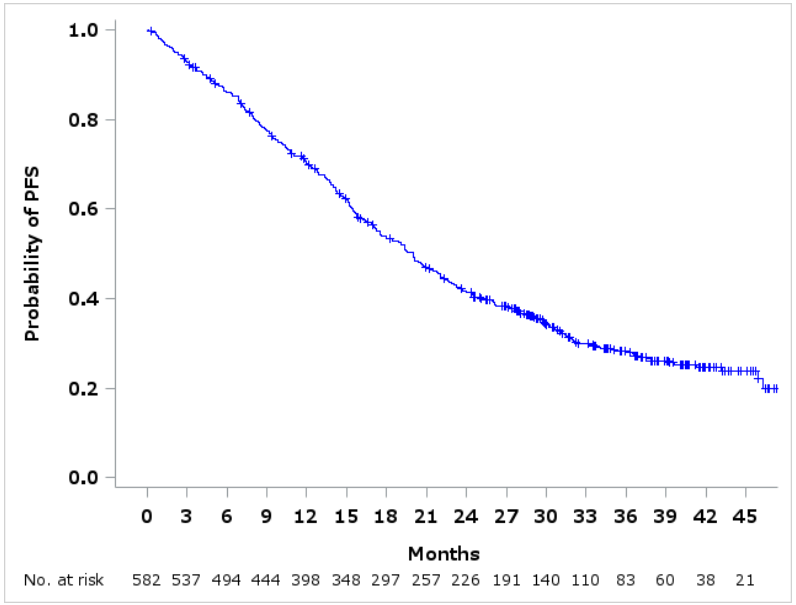
Overall response rate and disease control rate

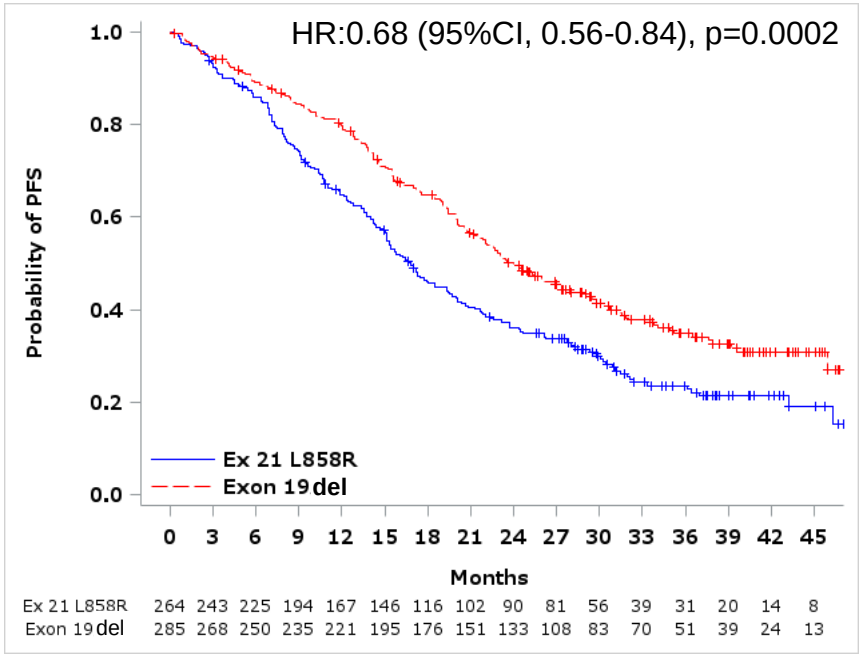
response	%
CR	3.4
PR	64.8
SD	18.7
PD	8.1
NE	5.0
Overall response rate	**68.3% (95%CI, 54.3-72.0)**
Disease control rate	**87.0% (95%CI, 84.0-89.6)**

Progression free survival

All	**20.0 months (95%CI, 17.6-21.7)**

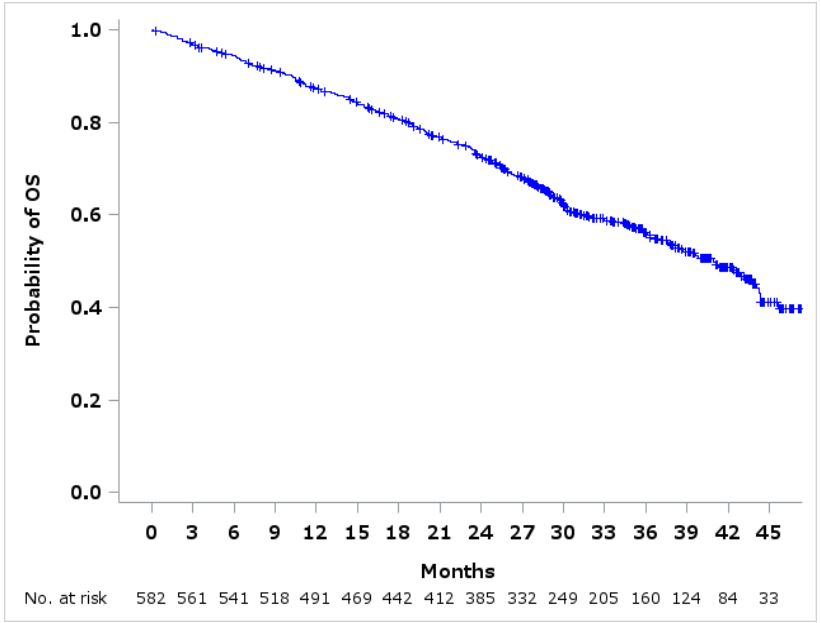
Ex19del	**23.5 months (95%CI, 21.3-28.0)**
L858R	**16.9 months (95%CI, 15.1-19.4)**



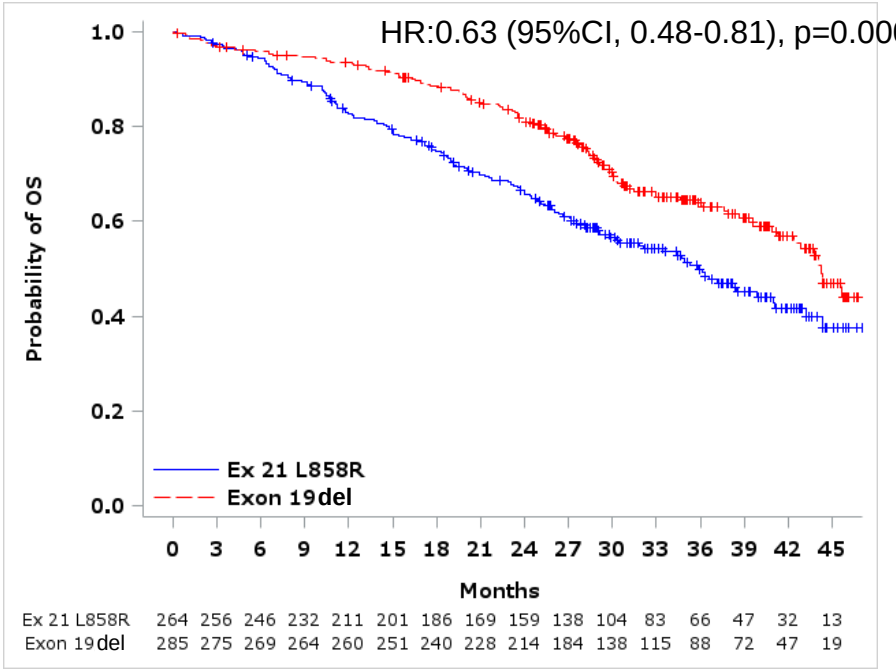


Overall survival

All	**41.0 months (95%CI, 37.1-44.1)**



Ex19del	**44.2 months (95%CI, 41.3-NA)**
L858R	**36.1 months (95%CI, 30.3-41.1)**



Course of treatment

Reason for discontinuation	n (%)
PD by RECIST	170 (29.2)
Clinical exacerbation	90 (15.4)
Adverse events	117 (20.1)
Patients' refusal	12 (2.1)
Judgment by attending physician	13 (2.2)
Others	45 (7.7)
(Ongoing treatment)	136 (23.3)

AE leading to discontinuation	n (%)
All events	**117 (20.1)**
Pneumonitis	61 (10.5)
Hematotoxicity	8 (1.4)
Rash*	7 (1.2)
Paronychia	6 (1.0)
AST/ALT increased	6 (1.0)
Anorexia	6 (1.0)
Prolonged QT interval	3 (0.5)
Diarrhea	2 (0.3)
Other	18 (3.1)

* Included rash acneiform, rash maculopapular, erythema multiforme and urticaria

Exacerbation pattern on RECIST PD

n (%)	Asymptomatic and no clinical exacerbation	Symptomatic and no clinical exacerbation	Clinical exacerbation*	Total
Central nervous system (CNS) metastasis only	16 (4.7%)	4 (1.2%)	17 (4.9%)	37 (10.8%)
Oligo-progression**	109 (31.7%)	30 (8.7%)	17 (4.9%)	156 (45.4%)
Multiple organs	70 (20.4%)	39 (11.3%)	42 (12.2%)	151 (43.9%)
Total	195 (56.7%)	73 (21.2%)	76 (22.1%)	344 (100%)

* Clinical exacerbation is defined as decline in PS and/or an exacerbation threatening major organs (carcinomatous lymphangiosis, bone marrow metastasis, carcinomatous meningitis, liver metastasis with liver damage, etc.)

** Single organ other than CNS (up to 3 per organ)

Percentage of patients who continued on osimertinib at the time of RECIST PD

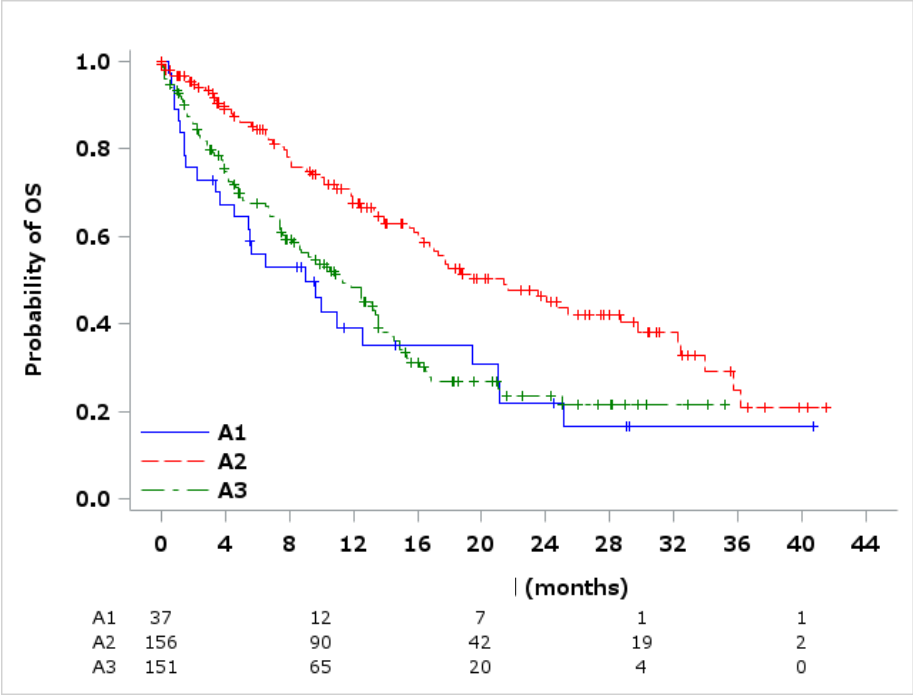
%（n/n）	Asymptomatic and no clinical exacerbation	Symptomatic and no clinical exacerbation	Clinical exacerbation*	Total
Central nervous system (CNS) metastasis only	87.5 (14/16)	75.0 (3/4)	47.1 (8/17)	67.6 (25/37)
Oligo-progression**	49.5 (54/109)	56.7 (17/30)	35.3 (6/17)	49.4 (77/156)
Multiple organs	55.7 (39/70)	35.9 (14/39)	19.0 (8/42)	40.4 (61/151)
Total	54.9 (107/195)	46.6 (34/73)	28.9 (22/76)	47.4 (163/344)

* Clinical exacerbation is defined as decline in PS and/or an exacerbation threatening major organs (carcinomatous lymphangiosis, bone marrow metastasis, carcinomatous meningitis, liver metastasis with liver damage, etc.)

** Single organ other than CNS (up to 3 per organ)

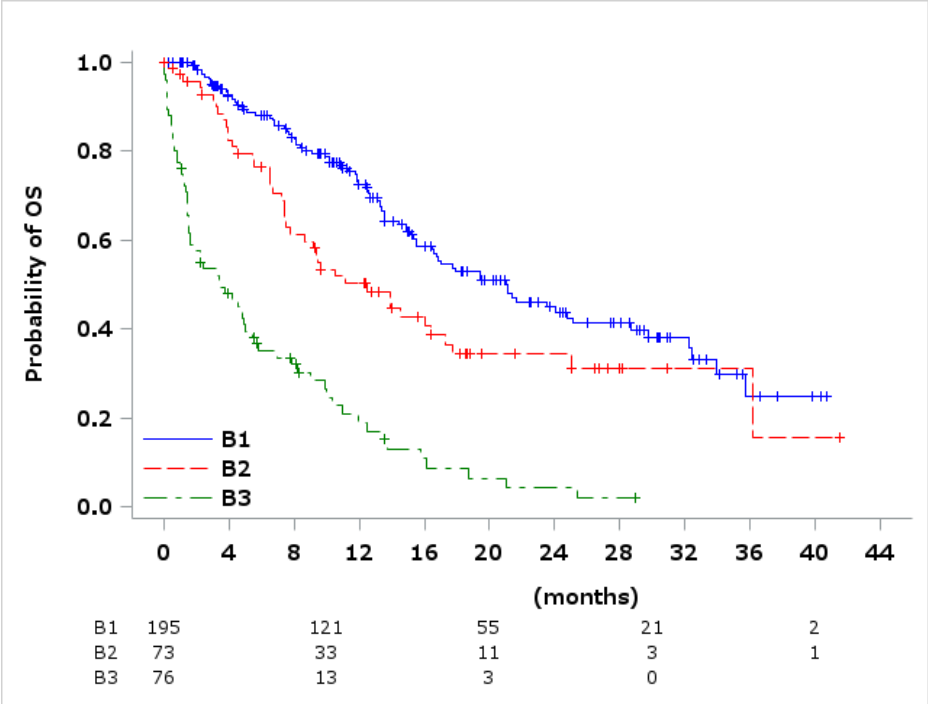
Survival after RECIST-PD with osimertinib

A1 CNS-only progression	9.0 months (95%CI, 3.7-19.4)
A2 oligo-progressions	21.4 months (95%CI, 16.4-29.7)
A3 multiple organ-progressions	11.3 months (95%CI, 8.3-13.5)



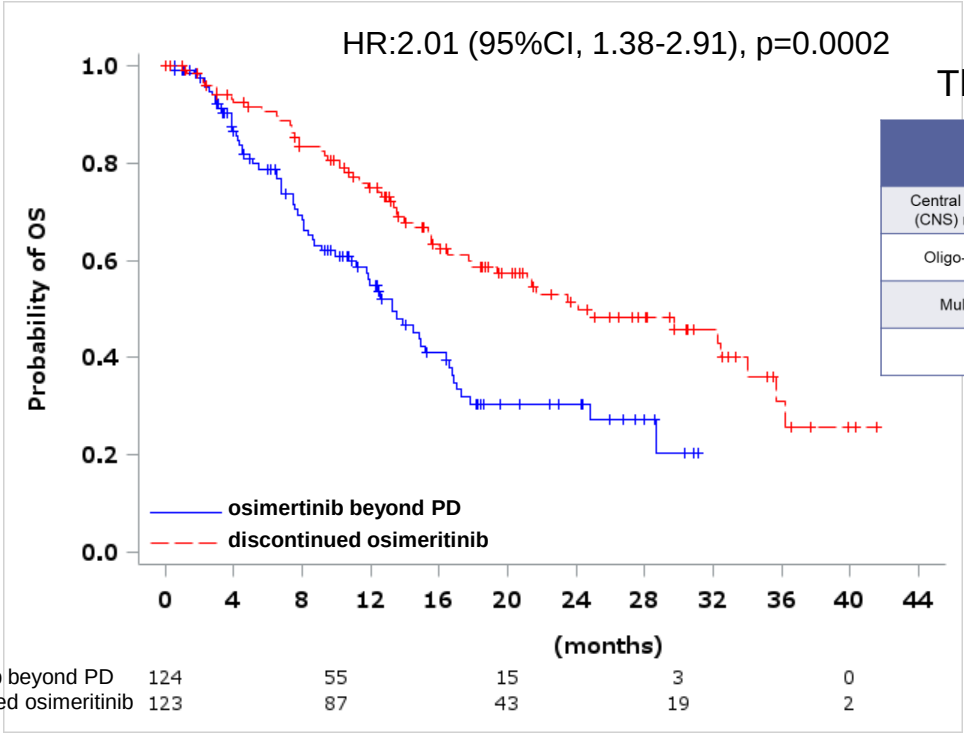
Survival after RECIST-PD with osimertinib

B1 Asymptomatic and no clinical exacerbation	21.1 months (95%CI, 16.5-28.7)
B2 Symptomatic and no clinical exacerbation	12.5 months (95%CI, 7.8-17.2)
B3 Clinical exacerbation	3.4 months (95%CI, 1.5-5.4)



Survival after RECIST-PD in a clinically stable population at the time of osimertinib RECIST-PD

osimertinib beyond PD	**13.3 months (95%CI, 10.9-16.4)**
discontinued osimertinib	**24.1 months (95%CI, 17.7-34.0)**



The clinically stable population is as follows.

n (%)	Asymptomatic and no clinical exacerbation	Symptomatic and no clinical exacerbation	Clinical exacerbation*	total
Central nervous system (CNS) metastasis only	16 (4.7%)	4 (1.2%)	17 (4.9%)	37 (10.8%)
Oligo-progression**	109 (31.7%)	30 (8.7%)	17 (4.9%)	156 (45.4%)
Multiple organs	70 (20.4%)	39 (11.3%)	42 (12.2%)	151 (43.9%)
Total	195 (56.7%)	73 (21.2%)	76 (22.1%)	344 (100%)

Adverse events

AE ≧ Grade 3	n (%)
All events	**136 (23.3)**
Pneumonitis	18 (3.1)
Rash*	18 (3.1)
AST/ALT increased	15 (2.6)
Anemia	13 (2.2)
Anorexia	12 (2.1)
Neutropenia	11 (1.9)
Paronychia	9 (1.5)
Diarrhea	6 (1.0)
Thrombocytopenia	5 (0.9)
Leukopenia	5 (0.9)
Prolonged QT interval	4 (0.7)

Pneumonitis	n (%)
Any grade	**75 (12.9)**
Grade 1	21 (3.6)
Grade 2	36 (6.2)
Grade 3	12 (2.1)
Grade 4	6 (1.0)
Grade 5	0 (0)

* Included rash acneiform, rash maculopapular, erythema multiforme and urticaria

Comparison with other trials

Trial	Area	Design	N	PFS (m)	OS (m)	ORR (%)	AE ≧ Grade 3 (%)
FLAURA	Global	Phase III trial	279	18.9	38.6	80	42
OSI-FACT	Japan	Retrospective cohort study	538	20.5	NR	79.8	NE
Reiwa (this study)	Japan	Prospective cohort study	583	20.0	41.0	68.3	23.3

NR: not reported
NE: not evaluated (?)

Conclusions

- First-line osimertinib showed good effectiveness in clinical practice, compatible with pivotal study results.
- Both PFS and OS were significantly better in patients with exon 19 deletion than those with exon21 L858R point mutation.
  (median PFS: 23.5 month vs. 16.9 months; median OS: 44.2 month vs. 36.1 months.)
- The progression patterns were CNS-only in 10.8%, oligo-progression in 45.4%, and multiple organ-progressions in 43.9%.
- 56.7% of the patients were asymptomatic at the time of RECIST PD.
- 47.7% of the patients continued to receive osimertinib beyond RECIST PD.
- Survival after RECIST PD in the clinically stable population was worse in the osimertinib continuation group than in the osimertinib discontinuation group.

References

1. Watanabe K, et al. BMJ Open. 2022 Jan 4;12(1):e046451.
2. Soria JC, et al. N Engl J Med. 2018 Jan 11;378(2):113-125.
3. Ramalingam SS, et al, N Engl J Med. 2020 Jan 2;382(1):41-50.
4. Sakata Y, et al, Eur J Cancer. 2021 Dec;159:144-153.

Funding:

This study was sponsored by the Public Health Research Foundation under the funding support from AstraZeneca.

Correspondence to:

Kageaki Watanabe, MD,

Department of Thoracic Oncology and RespiratoryMedicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital,

Bunkyo, Tokyo 113-8677, Japan

E-mail: kageaki_watanabe@tmhp.jp