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Efficacy and safety of first-line osimertinib treatment and post-progression patterns of care in patients with epidermal growth factor receptor activating mutation-positive advanced non-small-cell lung cancer (Reiwa study): design and rationale of a multicenter, real-world observational study

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1 **Title page**

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3 *Title*

4 Efficacy and safety of first-line osimertinib treatment and post-progression patterns of
5 care in patients with epidermal growth factor receptor activating mutation-positive
6 advanced non-small-cell lung cancer (Reiwa study): design and rationale of a multicenter,
7 real-world observational study

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19 55 Figures: 1

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24 57 **Keywords:** Osimertinib, EGFR-TKI, progression pattern, subsequent treatment,

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26 58 adherence, real-world data

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6 **60 ABSTRACT**

7
8 **61 Introduction:** Osimertinib, a third-generation epidermal growth factor receptor
9
10 **62 (EGFR)tyrosine kinase inhibitor (TKI), is widely used as the first-line treatment for EGFR**
11
12 **63 mutation-positive non-small cell lung cancer (NSCLC). Nevertheless, most cases**
13
14 **64 ultimately acquire resistance to osimertinib ultimately emerges, and no effective**
15
16 **65 treatment has been currently established for cases having progressive disease (PD) with**
17
18 **66 osimertinib. In clinical practice, EGFR-TKI therapy could be continued beyond RECIST**
19
20 **67 (response evaluation criteria in solid tumors)-defined PD cases when they are clinically**
21
22 **68 stable. Currently, the progression pattern of osimertinib and criteria for identifying**
23
24 **69 patients who might benefit from osimertinib beyond PD are unknown. In addition, the**
25
26 **70 efficacy and safety of osimertinib as the first-line treatment in real-world clinical practice**
27
28 **71 remain unclear in Japan. This multicenter study was designed to evaluate the real-world**
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30 **72 data on first-line osimertinib and its post-treatment.**
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37 **74 Methods and analysis:** The study enrolls patients with EGFR mutation-positive,
38
39 **75 advanced or recurrent NSCLC who received EGFR-TKI as the first-line therapy after**
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41 **76 September 1, 2018, from October 2019 to August 2020, and those started on osimertinib**
42
43 **77 will be followed up until August 2022. We will evaluate the efficacy and safety of the first-**
44
45 **78 line osimertinib treatment, adherence to it, progression patterns on RECIST PD, and**
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47 **79 subsequent treatment.**
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51 **80**
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53 **81 Ethics and dissemination:** All participating patients will provide written informed
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55 **82 consent before entering the study. The protocol, amendments, and patients' informed**
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57 **83 consent forms will be approved before study commencement by the institutional review**
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6 84 board or independent ethics committee at each participation site (Lead Ethics Committee.
7
8 85 Japan Red Cross Medical Center (26/04/2019, Order No. 976)) Patients will be
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10 86 anonymized before registration into the study and their anonymized data will be collected
11
12 87 from the case report form. The results of this study will be presented at the national and
13
14 88 international conferences and submitted for publication.
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20 90 **Trial registration number:** UMIN000038683
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23
24 92 **Keywords:** Osimertinib, EGFR-TKI, progression pattern, subsequent treatment,
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26 93 adherence, real-world data
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38 98 **Strengths and limitations of this study**

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40 99 •The strength of this study is that it is the first large, multicenter study in Japan to
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42 100 investigate osimertinib as the first-line treatment in real-world clinical practice.
43
44 101 •This study confirms the progression pattern of osimertinib and examines the optimal
45
46 102 subsequent treatment.
47
48 103 •The factors that make osimertinib less effective will be analyzed by identifying
49
50 104 medication adherence.
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52 105 •The classification of the progression pattern in this study is yet to be validated.
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54 106 •End points with small number of events might not be adequately analyzed.
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6 108 **TEXT**

7
8 109 **INTRODUCTION**

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10 110 Lung cancer is the most leading cause of cancer deaths in developed countries,
11 including Japan. In Japan, non-small cell lung cancer (NSCLC) accounts for
12 approximately 85% of all lung cancers, and among non-small cell cancers, approximately
13 111 approximately 85% of all lung cancers, and among non-small cell cancers, approximately
14 112 45% of adenocarcinomas are known to have activating mutations of the epidermal
15 113 growth factor receptor (EGFR) gene. [1] Patients with advanced or recurrent NSCLC with
16 114 EGFR mutations have been reported to be highly responsive to first- and second-
17 115 generation EGFR-tyrosine kinase inhibitors (TKIs); however, they become resistant to
18 116 EGFR-TKIs, and the median progression-free survival with EGFR-TKI is approximately
19 117 9–14 months.[2-5]

20 118
21 119 Notably, approximately half of the resistance was determined to be because of the
22 120 acquired T790M mutation, [6] and Osimertinib, a third-generation EGFR-TKI, was noted
23 121 to be effective against T790M mutation-positive lung cancer and was initially established
24 122 as the standard treatment for T790M mutation-positive lung cancer.[7] More recently,
25 123 osimertinib has been shown to provide a significantly longer progression-free survival
26 124 (PFS) and overall survival (OS) than the first-generation EGFR-TKI as the first-line
27 125 treatment for EGFR mutation-positive NSCLC, which has been noted to be more
28 126 effective and provided a longer PFS than the second-generation EGFR-TKI. [8,9]
29 127 Currently, osimertinib is widely used as the first-line treatment for EGFR mutation-
30 128 positive NSCLC with or without T790M mutation.

31 129 We have previously studied EGFR mutation-positive NSCLC in Japanese patients
32 130 treated with first- and second-generation EGFR-TKIs, such as gefitinib, erlotinib, and
33 131 afatinib after being diagnosed as progressive disease (PD) per the RECIST criteria. [10]
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6 132 In that study, when RECIST PD was determined, several patients were not clinically PD,
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8 133 and 35% of patients continued to receive EGFR-TKI. The median time from RECIST PD
9
10 134 to clinical PD or discontinuation of EGFR-TKI was 5 months, and no major differences
11
12 135 were observed regarding OS or survival after PD with RECIST related to continuing
13
14 136 EGFR-TKI treatment beyond PD than stopping EGFR-TKI treatment during RECIST PD.
15
16 137 Because several patients are clinically stable even after being diagnosed as RECIST
17
18 138 PD, EGFR-TKI therapy is often continued beyond PD in clinical practice. Moreover, it
19
20 139 has been reported that the addition of radiotherapy to EGFR-TKI could have favorable
21
22 140 outcomes, [11-15] if the progression site is limited to brain metastases only. [16,17]
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26 141 Most cases receiving osimertinib also ultimately acquire resistance to it, with the
27
28 142 median PFS of 19 months. [8] However, currently, no effective treatment has been
29
30 143 established for PD after osimertinib. In the Japanese subset of the FLAURA study, PFS
31
32 144 was prolonged with osimertinib compared to first-generation TKIs, but its initial
33
34 145 superiority in OS disappeared in the middle of the curve, which may be because of the
35
36 146 post-treatment effect of the first-line TKIs. [18]
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40 147 Clinicians have to decide when observing PD to osimertinib whether to discontinue or
41
42 148 continue the drug, or to switch to cytotoxic anticancer drug. Hence, information regarding
43
44 149 the progression pattern at the time of PD would be useful in deciding the optimal
45
46 150 treatment after osimertinib resistance. Progression patterns to TKIs could be divided into
47
48 151 progression of brain metastasis alone, progression of oligometastasis, systemic
49
50 152 progression,[19] progression on imaging alone, and clinical PD.[10] Per the former
51
52 153 classification, patients with brain metastasis alone or oligometastatic progression could
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54 154 continue osimertinib treatment with the addition of local therapy, [16,17] and in the latter
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56 155 classification, patients without clinical PD might continue osimertinib treatment beyond
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6 156 PD. However, currently, the progression patterns of osimertinib are not investigated, and
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8 157 neither the clinical relevance of “osimertinib beyond PD” nor criteria for identifying
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10 158 patients who would benefit from it is known. In addition, the efficacy and safety of
11
12 159 osimertinib as the first-line treatment in real-world clinical practice remains to be fully
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14 160 established in Japan, as is shown in the FLAURA Japanese subset data.

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16
17 161 In this study, we will survey the choice of EGFR-TKIs used as the first-line therapy in
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19 162 patients with advanced or recurrent EGFR mutation-positive NSCLC, and evaluate the
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21 163 efficacy and safety of osimertinib treatment in clinical practice, the progression patterns
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23 164 in RECIST PD with osimertinib, and subsequent treatment. In addition, we will examine
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25 165 the factors that make osimertinib less effective by identifying medication adherence.
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28 166 [20,21]

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32 33 168 **METHODS and ANALYSIS**

34 35 169 **Design**

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37 170 This observational study is a multicenter, prospective cohort study involving patients
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39 171 with EGFR mutation-positive advanced or recurrent NSCLC in Japan. The study does
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41 172 not include any particular intervention, patients will be managed using routine clinical
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43 173 care, and all treatments and examinations will be performed as in regular practice. The
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45 174 study will periodically survey and collect data on the registered patients using medical
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47 175 records. Overall, 35 institutions in Japan, including cancer centers, university hospitals,
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49 176 and community hospitals, participated in the study.

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53 54 178 **Patient and public involvement**

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57 179 There is no patient and public involved in the study. In principle, the results of the study
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6 180 will be disclosed if the research participant wishes to disclose the results of the study.
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10 182 **Study period**

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13 183 The study will be conducted from October 2019 to June 2023. Registration will take
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15 184 place from the approval date of ethical review at each institution to August 2020. The
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17 185 follow-up period will extend until August 2022 (2 years after the last patient was enrolled).
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19 186 Data entry and analysis will be completed by June 2023 (10 months after the last patient
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21 187 is observed).
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26 189 **Participants**

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28 190 Patients will be included in the study if they are aged ≥ 20 years and have advanced
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30 191 or recurrent metastatic NSCLC (the stage will be defined based on the UICC
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32 192 International Union for Tumors Lung Classifications [2017, 8th Edition]) that is EGFR
33
34 193 activating mutation-positive. Notably, any type of EGFR mutation will be acceptable. In
35
36 194 addition to Exon 19 deletion and Exon 21 L858R susceptibility gene mutations (common
37
38 195 mutations), rare EGFR mutations (uncommon mutations) will be eligible. Moreover, an
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40 196 additional eligibility criterion will be for patients to have started their first EGFR-TKI
41
42 197 treatment on or after September 1, 2018.
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46 198 Regarding EGFR-TKI treatment, patients who used anticancer drugs as local therapy
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48 199 like pleurodesis, patients treated with cytotoxic chemotherapy as prior therapy, patients
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50 200 treated with EGFR-TKIs and other anticancer drugs or angiogenesis inhibitors, patients
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52 201 who were primarily treated with EGFR-TKI as monotherapy and alternating between
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54 202 EGFR-TKI and other anticancer drugs, and patients who were enrolled in other clinical
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56 203 trials will also be deemed eligible.
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6 204 Patients who had started EGFR-TKI treatment before September 1, 2018, and patients
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8 205 deemed inappropriate for inclusion by each investigator will be excluded.
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11 207 **Research procedures**

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15 208 The investigators will select patient candidates, obtain written informed consent,
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17 209 complete the case registration form, and fax it to the data center. The data center will
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19 210 verify the patient's eligibility and register the patient based on the case registration form.

20
21 211 The patients will be classified into two groups based on the data provided at enrollment.
22
23 212 One group will comprise patients treated or to be treated with EGFR-TKI other than
24
25 213 osimertinib, and patients treated or to be treated with osimertinib in combination with
26
27 214 other anticancer drugs or angiogenesis inhibitors from the beginning of treatment. The
28
29 215 other group will comprise patients who started or will start osimertinib monotherapy.
30
31 216 Patients who have been receiving combination therapy with other anticancer drugs or
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33 217 angiogenesis inhibitors during the course of osimertinib treatment or who have been
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35 218 receiving replacement therapy with other anticancer drugs will be included in this group
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37 219 provided they were initially treated with osimertinib monotherapy.
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41 220 For the first group, the study will be completed at the time of enrollment survey with
42
43 221 confirmation of patient characteristics, details of EGFR-TKI therapy, and concomitant
44
45 222 drugs before initiation of EGFR-TKI therapy. In the second group, the study will continue
46
47 223 survey until the end of the study period. Each survey will include treatment details,
48
49 224 concomitant medications, imaging assessments, clinical exacerbations, flare events,
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51 225 adverse event reports, outcomes, and post-treatment details after osimertinib treatment.
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53 226 The investigators will conduct a simultaneous survey once every 6 months, using
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55 227 medical records from enrolled patients. The final survey will be conducted 2 years after
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6 228 the last patient was enrolled. The results of each study will be recorded in a continuing
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8 229 case report form for each study and sent to the data center.
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10 230 Patient-reported osimertinib compliance survey will be conducted in patients who were
11
12 231 started newly on osimertinib since the start of the study. Patients will be given a
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14 232 medication notebook, which they will fill out themselves, and a copy of the notebook will
15
16 233 be mailed to the data center 180 days after starting osimertinib with a medication
17
18 234 investigation report for each patient.
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21 235 All adverse events occurring during osimertinib treatment that are suspected to be
22
23 236 related to the treatment will be documented in the continuing case report form, regardless
24
25 237 of the severity. In the event of a serious adverse event, the standard reporting protocol
26
27 238 of a serious adverse event will be performed appropriately, including reporting to the
28
29 239 head of the medical institution and the authorities. In addition to that, the study mandates
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31 240 that the report be emailed to the administrative office within 24 hours and the primary
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33 241 report be emailed to the administrative office within 72 hours, using the “Emergency
34
35 242 Adverse Event Notification Form.” Finally, the administrative office will report the serious
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37 243 adverse event to the principal investigator of the study and AstraZeneca through email.
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43 44 245 **Data management and monitoring**

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46 246 Data will be centrally managed at the designated data center. Central monitoring will
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48 247 be performed to ensure that the study is conducted safely and in accordance with the
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50 248 protocol.
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54 55 250 **End point**

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57 251 This study’s primary endpoint is co-primary endpoint. First primary endpoint is PFS of
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6 252 osimertinib, time from the start of osimertinib to RECIST PD, or death from any cause.

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8 253 Another primary endpoint is percentage of patients with progression patterns listed below

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10 254 when RECIST PD was encountered with osimertinib treatment. This progression pattern

11
12 255 classification was modified from the paper by Goto Y et al [10]; however, this is yet to be

13
14 256 fully validated. Progression patterns are classified into nine categories (3 x 3) based on

15
16 257 progression site and patient status as follows:

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18 258 A. Progression patterns based on progression sites

19
20 259 (A1) Central nervous system only (including brain metastasis and carcinomatous

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22 260 meningitis)

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24 261 (A2) Oligometastasis (one to three lesions in one organ other than the brain)

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26 262 (A3) Progression in multiple organs (except A1 and A2)

27
28 263 B. Symptoms at exacerbation and exacerbation patterns per the patient's general

29
30 264 condition

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32 265 (B1) Asymptomatic, without progression as defined by B3

33
34 266 (B2) Symptomatic, without progression as defined by B3

35
36 267 (B3) Decreased PS or major organ threatening conditions (cancerous lymphangitis, bone

37
38 268 marrow metastasis, carcinomatous meningitis, hepatic metastasis with hepatic disorder,

39
40 269 etc.)

41
42 270 The study has several secondary endpoints, which are listed below.

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44 271 1. Response rate of osimertinib in patients with measurable lesions.

45
46 272 2. OS (time from the start of osimertinib to the date of death, irrespective of cause of

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48 273 death).

49
50 274 3. Percentage of patients who continued or discontinued osimertinib at RECIST PD.

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52 275 4. Number and type of drugs prescribed concomitantly with osimertinib (polypharmacy):

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6 276 oral drugs are classified and aggregated according to the type (gastrointestinal,
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8 277 antihypertensive, diabetic, etc.) and number (less than 5, 5–9, 10, or more).
9
10 278 5. Osimertinib adherence (survey of actual conditions using the medication handbook).
11
12
13 279 6. Duration of osimertinib treatment.
14
15 280 7. Percentage of patients who experienced flare, defined as rapid disease deterioration
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17 281 within 1 month resulting in hospitalization or death, after discontinuation of osimertinib
18
19 282 treatment, except in cases of infections, venous thrombosis, and other causes not
20
21 283 directly related to NSCLC exacerbation. [10]
22
23
24 284 8. Percentage of patients receiving concurrent chemotherapy or radiotherapy along with
25
26 285 osimertinib after osimertinib PD.
27
28 286 9. Percentage of patients who received chemotherapy after discontinuation of
29
30 287 osimertinib treatment.
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33 288 10. Percentage of patients re-administered osimertinib after more than 4 weeks of
34
35 289 discontinuation (if it is less than 4 weeks, it will be considered to be temporary interruption
36
37 290 rather than discontinuation).
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40 291 11. Percentage of patients with advanced or recurrent EGFR mutation-positive NSCLC
41
42 292 receiving osimertinib as initial therapy after September 2018 when osimertinib was
43
44 293 approved for use in patients with NSCLC untreated with EGFR-TKI in Japan.
45
46 294 12. Effects of osimertinib in patients with uncommon EGFR mutations.
47
48 295 13. Incidence of grade 3 or higher adverse events with osimertinib treatment.
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51 296 14. Incidence of pneumonitis caused by osimertinib.

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53 297 In addition, we will also perform exploratory analysis to investigate the content and
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55 298 efficacy of post-treatment after Osimertinib PD.
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6 300 **Sample size**
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8 301 Between September 2018 and August 2020, 700 patients were expected to be
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10 302 enrolled from 50 potential participating institutions. Of the 700 patients, the proportion of
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12 303 osimertinib was estimated to be 70% on average over 2 years, and the number of
13
14 304 patients treated with osimertinib was considered to be 500. Based on previous clinical
15
16 305 trial data, the median PFS for osimertinib is expected to be about 19 months. The study
17
18 306 has a 2-year enrollment period and a follow-up period of 2 years from the last patient's
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20 307 enrollment. Therefore, all 500 patients will be followed up for more than 2 years. For
21
22 308 PFS, which is one of the primary endpoints, we would expect events to occur in more
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24 309 than 60% of cases (number of events was 361, assuming a constant rate of enrollment
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26 310 over 2 years, minimum follow-up of 2 years, and an exponential distribution of median
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28 311 PFS of 19 months), and we believe that one of the primary endpoints, that is, the pattern
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30 312 of exacerbations, could be evaluated.
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37 314 **Data analysis**
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39 315 All efficacy analyses will be based on the full analysis set (and per protocol set for
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41 316 supportive analysis). The results of all statistical analyses will be performed using 95%
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43 317 confidence intervals and two-sided p values. Final analyses will be performed for all
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45 318 endpoints after the data have been finalized after the final investigation.
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48 319 PFS, OS, and duration of osimertinib treatment will be summarized using Kaplan-
49
50 320 Meier methods, and 95% confidence interval of median time will be calculated using
51
52 321 Brookmeyer and Crowley based on the log-log transformation of survival function. For
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54 322 PFS, we will perform subgroup analyses for the following covariates: gender (male,
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56 323 female), age (≥ 65 years, <65 years), primary disease (clinical stage, histology,
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6 324 metastatic organ), smoking history (yes, no), PS (0, 1), types of EGFR mutations,
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8 325 provided there is a certain number of events in each category. Regarding the percentage
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10 326 of patients with nine progression patterns as the primary endpoint, the percentage of
11
12 327 response rate and the percentage of patients with various secondary endpoints, the ratio
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14
15 328 and the 95% confidence interval of Clopper-Pearson will be calculated.
16

17 329

19 330 **Ethics and dissemination**

21 331 This study will be conducted per the principles of the Declaration of Helsinki and the
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23 332 Ethical Guidelines for Medical and Health Research Involving Human Subjects. All
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25 333 participating patients will provide written informed consent before entering the study.
26
27 334 However, informed consent will not be required for patients who are dead at the time of
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29 335 registration. The protocol, amendments, and patient informed consent forms will be
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31 336 approved by the institutional review board or the independent ethics committee at each
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33 337 participating site before study commencement. (Lead Ethics Committee. Japan Red
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35 338 Cross Medical Center (26/04/2019, Order No. 976))
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39 339 Furthermore, for data management and to ensure patient privacy, patients will be
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41 340 anonymized before registration and their anonymized data will be collected using the
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43 341 case report form. All personnel involved in the study will ensure confidentiality of all
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45 342 participating patients. The anonymization procedure planned is as follows: the
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47 343 investigators at each institution will give each participating patient an original number
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49 344 unique to the institution that is unrelated to the name and hospital ID of the patient, and
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51 345 register the patient in the data center using that original number. Subsequently, the data
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53 346 center will assign a registration number for this study. Each institution will prepare a list
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55 347 of correspondence between the original number of the institution and the registration
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6 348 number of this study, which will be strictly controlled by the institution. Enrolled patients
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8 349 are identified and queried using the registration number of this study. Information that
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10 350 can be used by a third party to directly identify a registered patient, such as the medical
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12 351 record numbers in clinical practice or the names and contact details of a registered
13
14 352 patient, will not be provided to the data center and not be registered at the data center.
15
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17 353 Data collected from patients in this study will not be used for any other purpose, and
18
19 354 potential information that discloses patient identity will not be published.
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23 24 356 **DISCUSSION**

25
26 357 This is the first study to evaluate the efficacy and safety of first-line osimertinib in real-
27
28 358 world clinical practice in Japan. Moreover, this study will determine the pattern of
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30 359 exacerbation of osimertinib in RECIST PD and investigate and analyze the real-world
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32 360 post-treatment. The study results will help identify the optimal treatment of patients with
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34 361 EGFR mutation-positive NSCLC based on the real-world exacerbation patterns after
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36 362 first-line osimertinib treatment.
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41 42 364 **CONCLUSION**

43
44 365 The results of this study will be presented at the national and international conferences
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46 366 and will be submitted for publication. We expect that all the data obtained and analyzed
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48 367 by this study will facilitate improved treatment strategies in the future for patients with
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50 368 EGFR mutation-positive lung cancer.
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370 Figure 1 Study schema, EGFR, epidermal growth factor receptor

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18
19 378 study. KW, YH, and HK drafted the protocol of the study. KW, KY, YH, KU, GN, KK, KU,
20
21 379 YO, and HK refined the study protocol and study implementation. All authors have read
22
23 380 and approved the final version of the manuscript.
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41
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43
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46 390 **Ethics approval:** Institutional review board or independent ethics committee at each
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48 391 participating site. (Lead Ethics Committee. Japan Red Cross Medical Center
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50 392 (26/04/2019, Order No. 976))
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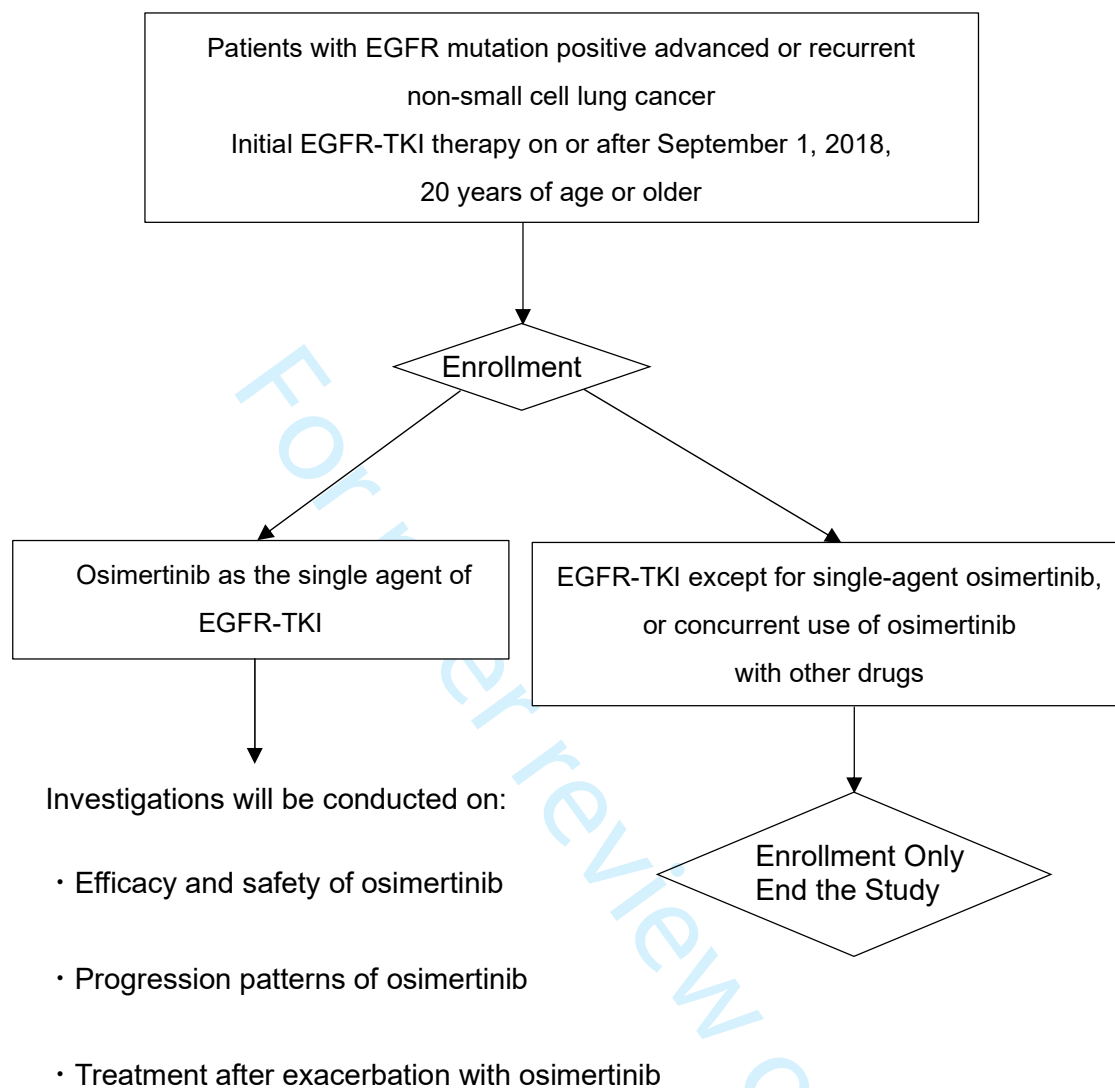
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BMJ Open

Efficacy and safety of first-line osimertinib treatment and post-progression patterns of care in patients with epidermal growth factor receptor activating mutation-positive advanced non-small-cell lung cancer (Reiwa study): study protocol of a multicenter, real-world observational study

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1 **Title page**

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3 *Title*

4 Efficacy and safety of first-line osimertinib treatment and post-progression patterns of
5 care in patients with epidermal growth factor receptor activating mutation-positive
6 advanced non-small-cell lung cancer (Reiwa study): study protocol of a multicenter, real-
7 world observational study

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15 53 Words: 3286
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19 55 Figures: 1
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24 57 **Keywords:** Osimertinib, EGFR-TKI, progression pattern, subsequent treatment,
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26 58 adherence, real-world data
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6 **60 ABSTRACT**

7
8 **61 Introduction:** Osimertinib, a third-generation epidermal growth factor receptor
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10 **62 (EGFR)tyrosine kinase inhibitor (TKI), is widely used as the first-line treatment for EGFR**
11
12 **63 mutation-positive non-small cell lung cancer (NSCLC). Nevertheless, most cases**
13
14 **64 ultimately acquire resistance to osimertinib ultimately emerges, and no effective**
15
16 **65 treatment has been currently established for cases having progressive disease (PD) with**
17
18 **66 osimertinib. In clinical practice, EGFR-TKI therapy could be continued beyond RECIST**
19
20 **67 (response evaluation criteria in solid tumors)-defined PD cases when they are clinically**
21
22 **68 stable. Currently, the progression pattern of osimertinib and criteria for identifying**
23
24 **69 patients who might benefit from osimertinib beyond PD are unknown. In addition, the**
25
26 **70 efficacy and safety of osimertinib as the first-line treatment in real-world clinical practice**
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28 **71 remain unclear in Japan. This multicenter study was designed to evaluate the real-world**
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30 **72 data on first-line osimertinib and its post-treatment.**
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37 **74 Methods and analysis:** The study enrolls patients with EGFR mutation-positive,
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39 **75 advanced or recurrent NSCLC who received EGFR-TKI as the first-line therapy after**
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41 **76 September 1, 2018, from October 2019 to August 2020, and those started on osimertinib**
42
43 **77 will be followed up until August 2022. We will evaluate the efficacy and safety of the first-**
44
45 **78 line osimertinib treatment, adherence to it, progression patterns on RECIST PD, and**
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47 **79 subsequent treatment.**
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51 **80**
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53 **81 Ethics and dissemination:** All participating patients will provide written informed
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55 **82 consent before entering the study. The protocol, amendments, and patients' informed**
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57 **83 consent forms will be approved before study commencement by the institutional review**
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6 84 board or independent ethics committee at each participation site (Lead Ethics Committee.
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8 85 Japan Red Cross Medical Center (26/04/2019, Order No. 976)) Patients will be
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10 86 anonymized before registration into the study and their anonymized data will be collected
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12 87 from the case report form. The results of this study will be presented at the national and
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14 88 international conferences and submitted for publication.
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20 90 **Trial registration number:** UMIN000038683
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24 92 **Keywords:** Osimertinib, EGFR-TKI, progression pattern, subsequent treatment,
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26 93 adherence, real-world data
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34 98 **Strengths and limitations of this study**

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39 99 •The strength of this study is that it is the first large, multicenter study in Japan to
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41 100 investigate osimertinib as the first-line treatment in real-world clinical practice.
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44 101 •This study confirms the progression pattern of osimertinib and examines the optimal
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46 102 subsequent treatment.
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48 103 •The factors that make osimertinib less effective will be analyzed by identifying
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50 104 medication adherence.
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52 105 •The classification of the progression pattern in this study is yet to be validated.
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54 106 •End points with small number of events might not be adequately analyzed.
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6 108 **TEXT**

7
8 109 **INTRODUCTION**

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10 110 Lung cancer is the most leading cause of cancer deaths in developed countries,
11 including Japan. In Japan, non-small cell lung cancer (NSCLC) accounts for
12 approximately 85% of all lung cancers, and among non-small cell cancers, approximately
13 111 approximately 85% of all lung cancers, and among non-small cell cancers, approximately
14 112 approximately 85% of all lung cancers, and among non-small cell cancers, approximately
15 113 45% of adenocarcinomas are known to have activating mutations of the epidermal
16 114 growth factor receptor (EGFR) gene. [1] Patients with advanced or recurrent NSCLC with
17 115 EGFR mutations have been reported to be highly responsive to first- and second-
18 116 generation EGFR-tyrosine kinase inhibitors (TKIs); however, they become resistant to
19 117 EGFR-TKIs, and the median progression-free survival with EGFR-TKI is approximately
20 118 9–14 months.[2-5]

21
22 119 Notably, approximately half of the resistance was determined to be because of the
23 120 acquired T790M mutation, [6] and Osimertinib, a third-generation EGFR-TKI, was noted
24 121 to be effective against T790M mutation-positive lung cancer and was initially established
25 122 as the standard treatment for T790M mutation-positive lung cancer.[7] More recently,
26 123 osimertinib has been shown to provide a significantly longer progression-free survival
27 124 (PFS) and longer overall survival (OS) than the first-generation EGFR-TKI as the first-
28 125 line treatment for EGFR mutation-positive NSCLC, which has been noted to be more
29 126 effective and provided a longer PFS than the second-generation EGFR-TKI. [8,9]
30 127 Currently, osimertinib is widely used as the first-line treatment for EGFR mutation-
31 128 positive NSCLC with or without T790M mutation.

32
33 129 We have previously studied EGFR mutation-positive NSCLC in Japanese patients
34 130 treated with first- and second-generation EGFR-TKIs, such as gefitinib, erlotinib, and
35 131 afatinib after being diagnosed as progressive disease (PD) per the RECIST criteria. [10]
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6 132 In that study, when RECIST PD was determined, several patients were not clinically PD,
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8 133 and 35% of patients continued to receive EGFR-TKI. The median time from RECIST PD
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10 134 to clinical PD or discontinuation of EGFR-TKI was 5 months, and no major differences
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12 135 were observed regarding OS or survival after PD with RECIST related to continuing
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14 136 EGFR-TKI treatment beyond PD than stopping EGFR-TKI treatment during RECIST PD.
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16 137 Because several patients are clinically stable even after being diagnosed as RECIST
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18 138 PD, EGFR-TKI therapy is often continued beyond PD in clinical practice. Moreover, it
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20 139 has been reported that the addition of radiotherapy to EGFR-TKI could have favorable
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22 140 outcomes, [11-15] if the progression site is limited to brain metastases only. [16,17]

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26 141 Most cases receiving osimertinib also ultimately acquire resistance to it, with the
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28 142 median PFS of 19 months. [8] However, currently, no effective treatment has been
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30 143 established for PD after osimertinib. In the Japanese subset of the FLAURA study, PFS
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32 144 was prolonged with osimertinib compared to first-generation TKIs, but its initial
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34 145 superiority in OS disappeared in the middle of the curve, which may be because of the
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36 146 post-treatment effect of the first-line TKIs. [18]

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39 147 Clinicians have to decide when observing PD to osimertinib whether to discontinue or
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41 148 continue the drug, or to switch to cytotoxic anticancer drug. Hence, information regarding
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43 149 the progression pattern at the time of PD would be useful in deciding the optimal
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45 150 treatment after osimertinib resistance. Yang et al. reported that the clinical mode of
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47 151 failure of EGFR-TKIs can favor strategies for subsequent treatment and predict survival
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49 152 benefit in advanced NSCLC. [19] Progression patterns to TKIs could be divided into
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51 153 progression of brain metastasis alone, progression of oligometastasis, systemic
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53 154 progression,[20] progression on imaging alone, and clinical PD.[10] Per the former
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55 155 classification, patients with brain metastasis alone or oligometastatic progression could
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6 156 continue osimertinib treatment with the addition of local therapy, [16,17] and in the latter
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8 157 classification, patients without clinical PD might continue osimertinib treatment beyond
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10 158 PD. However, currently, the progression patterns of osimertinib are not investigated, and
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12
13 159 neither the clinical relevance of “osimertinib beyond PD” nor criteria for identifying
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15 160 patients who would benefit from it is known. In addition, the efficacy and safety of
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17 161 osimertinib as the first-line treatment in real-world clinical practice remains to be fully
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19 162 established in Japan, as is shown in the FLAURA Japanese subset data.

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21
22 163 In this study, we will survey the choice of EGFR-TKIs used as the first-line therapy in
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24 164 patients with advanced or recurrent EGFR mutation-positive NSCLC, and evaluate the
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26 165 efficacy and safety of osimertinib treatment in clinical practice, the progression patterns
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28 166 in RECIST PD with osimertinib, and subsequent treatment. In addition, we will examine
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30 167 the factors that make osimertinib less effective by identifying medication adherence.
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36 37 170 **METHODS and ANALYSIS**

38 39 171 **Design**

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42 172 This observational study is a multicenter, prospective cohort study involving patients
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44 173 with EGFR mutation-positive advanced or recurrent NSCLC in Japan. The study does
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46 174 not include any particular intervention, patients will be managed using routine clinical
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48 175 care, and all treatments and examinations will be performed as in regular practice. The
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50 176 study will periodically survey and collect data on the registered patients using medical
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52 177 records. Overall, 35 institutions in Japan, including cancer centers, university hospitals,
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54 178 and community hospitals, participated in the study.
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180 **Patient and public involvement**

181 There is no patient and public involved in the study. In principle, the results of the study
182 will be disclosed if the research participant wishes to disclose the results of the study.

184 **Study period**

185 The study will be conducted from October 2019 to June 2023. Registration will take
186 place from the approval date of ethical review at each institution to August 2020. The
187 follow-up period will extend until August 2022 (2 years after the last patient was enrolled).
188 Data entry and analysis will be completed by June 2023 (10 months after the last patient
189 is observed).

191 **Participants**

192 Patients will be included in the study if they are aged ≥ 20 years and have advanced
193 or recurrent metastatic NSCLC (the stage will be defined based on the UICC
194 International Union for Tumors Lung Classifications [2017, 8th Edition]) that is EGFR
195 activating mutation-positive. Recurrent metastatic NSCLC is defined as patients who
196 cannot be treated with local treatments alone and require systemic chemotherapy with
197 EGFR-TKIs. Notably, any type of EGFR mutation will be acceptable. In addition to Exon
198 19 deletion and Exon 21 L858R susceptibility gene mutations (common mutations), rare
199 EGFR mutations (uncommon mutations) will be eligible. Moreover, an additional
200 eligibility criterion will be for patients to have started their first EGFR-TKI treatment on or
201 after September 1, 2018.

202 Regarding EGFR-TKI treatment, patients who used anticancer drugs as local therapy
203 like pleurodesis, patients treated with cytotoxic chemotherapy as prior therapy, patients

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6 204 treated with EGFR-TKIs and other anticancer drugs or angiogenesis inhibitors, patients
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8 205 who were primarily treated with EGFR-TKI as monotherapy and alternating between
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10 206 EGFR-TKI and other anticancer drugs, and patients who were enrolled in other clinical
11
12 207 trials will also be deemed eligible.

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15 208 Patients who had started EGFR-TKI treatment before September 1, 2018, and patients
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17 209 deemed inappropriate for inclusion by each investigator will be excluded.

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21 211 **Research procedures**

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24 212 The investigators will select patient candidates, obtain written informed consent,
25
26 213 complete the case registration form, and fax it to the data center. The data center will
27
28 214 verify the patient's eligibility and register the patient based on the case registration form.

29
30 215 The patients will be classified into two groups based on the data provided at enrollment
31
32 216 (figure 1). One group will comprise patients treated or to be treated with EGFR-TKI other
33
34 217 than osimertinib, and patients treated or to be treated with osimertinib in combination
35
36 218 with other anticancer drugs or angiogenesis inhibitors from the beginning of treatment.

37
38 219 The other group will comprise patients who started or will start osimertinib monotherapy.
39
40 220 Patients who have been receiving combination therapy with other anticancer drugs or
41
42 221 angiogenesis inhibitors during the course of osimertinib treatment or who have been
43
44 222 receiving replacement therapy with other anticancer drugs will be included in this group
45
46 223 provided they were initially treated with osimertinib monotherapy.

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49 224 For the first group, the study will be completed at the time of enrollment survey with
50
51 225 confirmation of patient characteristics, details of EGFR-TKI therapy, and concomitant
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53 226 drugs before initiation of EGFR-TKI therapy. In the second group, the study will continue
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55 227 survey until the end of the study period. Each survey will include treatment details,
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6 228 concomitant medications, imaging assessments, clinical exacerbations, flare events,
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8 229 adverse event reports, outcomes, and post-treatment details after osimertinib treatment.
9
10 230 The investigators will conduct a simultaneous survey once every 6 months, using
11
12 231 medical records from enrolled patients. The final survey will be conducted 2 years after
13
14 232 the last patient was enrolled. The results of each study will be recorded in a continuing
15
16 233 case report form for each study and sent to the data center.
17
18

19 234 Patient-reported osimertinib compliance survey will be conducted in patients who were
20
21 235 started newly on osimertinib since the start of the study. Patients will be given a
22
23 236 medication notebook, which they will fill out themselves, and a copy of the notebook will
24
25 237 be mailed to the data center 180 days after starting osimertinib with a medication
26
27 238 investigation report for each patient.
28
29

30 239 All adverse events occurring during osimertinib treatment that are suspected to be
31
32 240 related to the treatment will be documented in the continuing case report form, regardless
33
34 241 of the severity. In the event of a serious adverse event, the standard reporting protocol
35
36 242 of a serious adverse event will be performed appropriately, including reporting to the
37
38 243 head of the medical institution and the authorities. In addition to that, the study mandates
39
40 244 that the report be emailed to the administrative office within 24 hours and the primary
41
42 245 report be emailed to the administrative office within 72 hours, using the “Emergency
43
44 246 Adverse Event Notification Form.” Finally, the administrative office will report the serious
45
46 247 adverse event to the principal investigator of the study and AstraZeneca through email.
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52 53 249 **Data management and monitoring**

54
55 250 Data will be centrally managed at the designated data center. Central monitoring will
56
57 251 be performed to ensure that the study is conducted safely and in accordance with the
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6 252 protocol.

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10 254 **End point**

11
12 255 This study's primary endpoint is co-primary endpoint. First primary endpoint is PFS of
13 osimertinib, time from the start of osimertinib to RECIST PD, or death from any cause.

14
15 256 Another primary endpoint is percentage of patients with progression patterns listed below

16
17 257 when RECIST PD was encountered with osimertinib treatment. This progression pattern

18
19 258 classification was modified from the paper by Goto Y et al [10]; however, this is yet to be

20
21 259 fully validated. Progression patterns are classified into nine categories (3 x 3) based on

22
23 260 progression site and patient status as follows:

24
25 261 A. Progression patterns based on progression sites

26
27 262 (A1) Central nervous system only (including brain metastasis and carcinomatous
28 meningitis)

29
30 263 (A2) Oligometastasis (one to three lesions in one organ other than the brain)

31
32 264 (A3) Progression in multiple organs (except A1 and A2)

33
34 265 B. Symptoms at exacerbation and exacerbation patterns per the patient's general
35 condition

36
37 266 (B1) Asymptomatic, without progression as defined by B3 (This pattern is applied when a
38 patient has PD on RECIST due to the appearance of a new lesion or the enlargement of a
39 target or non-target lesion, but the appearance or enlargement of the lesion is asymptomatic
40 and the patient has no symptoms.)

41
42 267 (B2) Symptomatic, without progression as defined by B3

43
44 268 (B3) Decreased PS or major organ threatening conditions (cancerous lymphangitis, bone
45 marrow metastasis, carcinomatous meningitis, hepatic metastasis with hepatic disorder,
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6 276 etc.)

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8 277 The study has several secondary endpoints, which are listed below.

9
10 278 1. Response rate of osimertinib in patients with measurable lesions.

11
12 279 2. OS (time from the start of osimertinib to the date of death, irrespective of cause of
13
14 280 death).

15
16 281 3. Percentage of patients who continued or discontinued osimertinib at RECIST PD.

17
18 282 4. Number and type of drugs prescribed concomitantly with osimertinib (polypharmacy):

19
20 283 oral drugs are classified and aggregated according to the type (gastrointestinal,

21
22 284 antihypertensive, diabetic, etc.) and number (less than 5, 5–9, 10, or more).

23
24 285 5. Osimertinib adherence (survey of actual conditions using the medication handbook).

25
26 286 6. Duration of osimertinib treatment.

27
28 287 7. Percentage of patients who experienced flare, defined as rapid disease deterioration

29
30 288 within 1 month resulting in hospitalization or death, after discontinuation of osimertinib

31
32 289 treatment, except in cases of infections, venous thrombosis, and other causes not

33
34 290 directly related to NSCLC exacerbation. [10]

35
36 291 8. Percentage of patients receiving concurrent chemotherapy or radiotherapy along with

37
38 292 osimertinib after osimertinib PD.

39
40 293 9. Percentage of patients who received chemotherapy after discontinuation of

41
42 294 osimertinib treatment.

43
44 295 10. Percentage of patients re-administered osimertinib after more than 4 weeks of

45
46 296 discontinuation (if it is less than 4 weeks, it will be considered to be temporary interruption

47
48 297 rather than discontinuation).

49
50 298 11. Percentage of patients with advanced or recurrent EGFR mutation-positive NSCLC

51
52 299 receiving osimertinib as initial therapy after September 2018 when osimertinib was

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6 300 approved for use in patients with NSCLC untreated with EGFR-TKI in Japan.
7

8 301 12. Effects of osimertinib in patients with uncommon EGFR mutations.
9

10 302 13. Incidence of grade 3 or higher adverse events with osimertinib treatment.
11

12 303 14. Incidence of pneumonitis caused by osimertinib.
13

14 304 Effects of osimertinib in patients with uncommon EGFR mutations will be analyzed
15

16 305 within secondary endpoint 12, and other efficacy endpoints will be analyzed for common
17

18 306 EGFR activating mutations.
19

20 307 In addition, we will also perform exploratory analysis to investigate the content and
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22 308 efficacy of post-treatment after Osimertinib PD.
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26 310 **Sample size**
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28 311 Between September 2018 and August 2020, 700 patients were expected to be
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30 312 enrolled from 50 potential participating institutions. Of the 700 patients, the proportion of
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32 313 osimertinib was estimated to be 70% on average over 2 years, and the number of
33

34 314 patients treated with osimertinib was considered to be 500. Based on previous clinical
35

36 315 trial data, the median PFS for osimertinib is expected to be about 19 months. The study
37

38 316 has a 2-year enrollment period and a follow-up period of 2 years from the last patient's
39

40 317 enrollment. Therefore, all 500 patients will be followed up for more than 2 years. For
41

42 318 PFS, which is one of the primary endpoints, we would expect events to occur in more
43

44 319 than 60% of cases (number of events was 361, assuming a constant rate of enrollment
45

46 320 over 2 years, minimum follow-up of 2 years, and an exponential distribution of median
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48 321 PFS of 19 months), and we believe that one of the primary endpoints, that is, the pattern
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50 322 of exacerbations, could be evaluated.
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324 **Data analysis**

325 All efficacy analyses will be based on the full analysis set (and per protocol set for
326 supportive analysis). The results of all statistical analyses will be performed using 95%
327 confidence intervals and two-sided p values. Final analyses will be performed for all
328 endpoints after the data have been finalized after the final investigation.

329 PFS, OS, and duration of osimertinib treatment will be summarized using Kaplan-
330 Meier methods, and 95% confidence interval of median time will be calculated using
331 Brookmeyer and Crowley based on the log-log transformation of survival function. For
332 PFS, we will perform subgroup analyses for the following covariates: gender (male,
333 female), age (≥ 65 years, <65 years), primary disease (clinical stage, histology,
334 metastatic organ), smoking history (yes, no), PS (0, 1), types of EGFR mutations,
335 provided there is a certain number of events in each category. Regarding the percentage
336 of patients with nine progression patterns as the primary endpoint, the percentage of
337 response rate and the percentage of patients with various secondary endpoints, the ratio
338 and the 95% confidence interval of Clopper-Pearson will be calculated.

339

340 **Ethics and dissemination**

341 This study will be conducted per the principles of the Declaration of Helsinki and the
342 Ethical Guidelines for Medical and Health Research Involving Human Subjects. All
343 participating patients will provide written informed consent before entering the study.
344 However, informed consent will not be required for patients who are dead at the time of
345 registration. The protocol, amendments, and patient informed consent forms will be
346 approved by the institutional review board or the independent ethics committee at each
347 participating site before study commencement. (Lead Ethics Committee. Japan Red

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6 348 Cross Medical Center (26/04/2019, Order No. 976))
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8 349 Furthermore, for data management and to ensure patient privacy, patients will be
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10 350 anonymized before registration and their anonymized data will be collected using the
11
12 351 case report form. All personnel involved in the study will ensure confidentiality of all
13
14 352 participating patients. The anonymization procedure planned is as follows: the
15
16 353 investigators at each institution will give each participating patient an original number
17
18 354 unique to the institution that is unrelated to the name and hospital ID of the patient, and
19
20 355 register the patient in the data center using that original number. Subsequently, the data
21
22 356 center will assign a registration number for this study. Each institution will prepare a list
23
24 357 of correspondence between the original number of the institution and the registration
25
26 358 number of this study, which will be strictly controlled by the institution. Enrolled patients
27
28 359 are identified and queried using the registration number of this study. Information that
29
30 360 can be used by a third party to directly identify a registered patient, such as the medical
31
32 361 record numbers in clinical practice or the names and contact details of a registered
33
34 362 patient, will not be provided to the data center and not be registered at the data center.
35
36 363 Data collected from patients in this study will not be used for any other purpose, and
37
38 364 potential information that discloses patient identity will not be published.
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47 366 **DISCUSSION**

48 367 This is the first study to evaluate the efficacy and safety of first-line osimertinib in real-
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50 368 world clinical practice in Japan. Moreover, this study will determine the pattern of
51
52 369 exacerbation of osimertinib in RECIST PD and investigate and analyze the real-world
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54 370 post-treatment. The study results will help identify the optimal treatment of patients with
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56 371 EGFR mutation-positive NSCLC based on the real-world exacerbation patterns after
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6 372 first-line osimertinib treatment. The results of this study will be presented at the national
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8 373 and international conferences and will be submitted for publication. We expect that all
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10 374 the data obtained and analyzed by this study will facilitate improved treatment strategies
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13 375 in the future for patients with EGFR mutation-positive lung cancer.
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For peer review only

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6 377 Figure 1 Study schema, EGFR, epidermal growth factor receptor
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16
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18
19 385 study. KW, YH, and HK drafted the protocol of the study. KW, KY, YH, KU, GN, KK, KU,
20
21 386 YO, and HK refined the study protocol and study implementation. All authors have read
22
23 387 and approved the final version of the manuscript.
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29
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31 390

32
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34
35 392 data verification, or the statistical analysis.
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41
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45 396

46 397 **Ethics approval:** Institutional review board or independent ethics committee at each
47
48 398 participating site. (Lead Ethics Committee. Japan Red Cross Medical Center
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50 399 (26/04/2019, Order No. 976))
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