

Osimertinib in Elderly Patients with Epidermal Growth Factor Receptor T790M-Positive Non-Small-Cell Lung Cancer Who Progressed During Prior Treatment: A Phase II Trial

AKIRA NAKAO,^{a,†} OSAMU HIRANUMA,^{b,†} JUNJI UCHINO,^{c,†} CHIKARA SAKAGUCHI,^d TOSHIYUKI KITA,^e NORIYA HIRAOKA,^f TAMOTSU ISHIZUKA,^g YUTAKA KUBOTA,^h MASAYUKI KAWASAKI,ⁱ YASUHIRO GOTO,^j HISAO IMAI,^k NOBORU HATTORI,^l KEITA NAKATOMI,^m HIDETAKA URAMOTO,ⁿ KIYOAKI URYU,^o MINORU FUKUDA,^p YASUKI UCHIDA,^q TOSHIHIDE YOKOYAMA,^r MASAYA AKAI,^s TADASHI MIO,^t SEIJI NAGASHIMA,^u YUSUKE CHIHARA,^c NOBUYO TAMIYA,^c YOSHIKO KANEKO,^c TAKAKO MOURI,^c TADAOKI YAMADA,^c KENICHI YOSHIMURA,^v MASAKI FUJITA,^a KOICHI TAKAYAMA^c

^aDepartment of Respiratory Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan; ^bDepartment of Respiratory Medicine, Otsu City Hospital, Shiga, Japan; ^cDepartment of Pulmonary Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; ^dDepartment of Pulmonary Medicine, Rakuwakai Otowa Hospital, Kyoto, Japan; ^eDepartment of Respiratory Medicine, National Hospital Organization, Kanazawa Medical Center, Ishikawa, Japan; ^fDepartment of Respiratory Medicine, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan; ^gThird Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Fukui, Japan; ^hDepartment of Respiratory Medicine, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan; ⁱDepartment of Respiratory Medicine, National Hospital Organization, Omuta Hospital, Fukuoka, Japan; ^jDepartment of Respiratory Medicine, Fujita Health University, Aichi, Japan; ^kDivision of Respiratory Medicine, Gunma Prefectural Cancer Center, Gunma, Japan; ^lDepartment of Molecular and Internal Medicine, Institute of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan; ^mDepartment of Respiratory Medicine, Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuoka, Japan; ⁿDepartment of Thoracic Surgery, Kanazawa Medical University, Ishikawa, Japan; ^oDepartment of Respiratory Medicine, Yao Tokushukai General Hospital, Osaka, Japan; ^pSecond Department of Internal Medicine, Nagasaki University Hospital, Nagasaki, Japan; ^qDepartment of Respiratory Medicine, Shiga University of Medical Science Hospital, Shiga, Japan; ^rDepartment of Respiratory Medicine, Kurashiki Central Hospital, Okayama, Japan; ^sDepartment of Respiratory Medicine, Japanese Red Cross Fukui Hospital, Fukui, Japan; ^tDivision of Respiratory Medicine, Center for Respiratory Diseases, National Hospital Organization Kyoto Medical Center, Kyoto, Japan; ^uDepartment of Respiratory Medicine, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan; ^vDepartment of Biostatistics, Innovative Clinical Research Center, Kanazawa University, Ishikawa, Japan

[†]Contributed equally

TRIAL INFORMATION

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- **Sponsor(s):** AstraZeneca
- **Principal Investigator:** Junji Uchino
- **IRB Approved:** Yes

LESSONS LEARNED

- Non-small-cell lung cancer (NSCLC) represents 85% of lung cancer in elderly patients.
- In the present study performed in the 36 elderly subjects with epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC, osimertinib 80 mg demonstrated statistically significant improvement in the objective response rate, which was comparable to those in the nonelderly population.
- Osimertinib appears to be an effective and safe treatment option in elderly patients with advanced NSCLC with EGFR mutation; further research in larger scale is warranted.

ABSTRACT

Background. Previous findings suggest the possibility of relatively safe use of osimertinib for patients with T790M-positive non-small-cell lung cancer (NSCLC), with few serious adverse

events for the elderly in comparison with conventional endothelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), and with an antitumor effect.

Correspondence: Junji Uchino, M.D., Ph.D., Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, 465 Kajji-cho, Kamigyo-ku, Kyoto, Japan 6028566. Telephone: 81-75-251-5513; e-mail: uchino@koto.kpu-m.ac.jp Received December 10, 2018; accepted for publication December 29, 2018; published Online First on January 16, 2019. © AlphaMed Press; the data published online to support this summary are the property of the authors. <http://dx.doi.org/10.1634/theoncologist.2019-0003>

Methods. This phase II study was performed to prospectively investigate the efficacy and safety of osimertinib for elderly patients aged ≥ 75 years with ineffective prior EGFR TKI treatment or with recurrence in T790M EGFR TKI resistance mutation-positive NSCLC.

Results. A total of 36 patients were included in the analyses. Among the 36 subjects, 63.9% were female, with mean age of 79.9 years. The objective response rate (ORR) was 58.3% (95% confidence interval [CI], 42.2%–72.9%), demonstrating statistically significant efficacy of osimertinib ($p = .0017$). The median duration of response (DOR) was 27.9 weeks (95% CI, 21.1–82.0). Complete response (CR) and partial response (PR) were 2.8% and 55.6%, respectively. Disease control rate (DCR) was 97.2%. A waterfall plot revealed that 33 (91.6%) subjects exhibited tumor shrinkage during treatment, including 12 of 14 subjects who had stable disease (SD). All adverse events were not reason for discontinuation of the study drug.

Conclusion. Osimertinib may be an effective and safe treatment option in elderly patients with advanced NSCLC with EGFR mutation. *The Oncologist* 2019;24:593–e170

DISCUSSION

Lung cancer is the most common malignancy, accounting for 12.9% of all new cancer diagnoses, and the most common cause of cancer deaths [1]. Median age at diagnosis of lung cancer has been reported to be 63–70 years [2–6], and NSCLC represents 85% of lung cancer in elderly patients [7–9]. Treatment of elderly patients requires particular care for several reasons. Elderly patients typically have more comorbidities than younger patients, requiring concurrent management. Physiological functions decline with aging, such that some patients tolerate therapy more poorly. Furthermore, concurrent noncancer therapies may interfere with the metabolism of chemotherapeutic drugs. Afatinib, a second-generation EGFR TKI, showed a proliferation-inhibitory effect on a lung cancer cell strain that had T790M mutation [10]; however, as for safety in the elderly, the medical evidence is not yet clear, unlike that for the first-generation EGFR TKI.

Osimertinib, a third-generation EGFR TKI that irreversibly inhibits EGFR, demonstrates inhibitory activity against tumor cells harboring sensitizing EGFR mutations and also selective

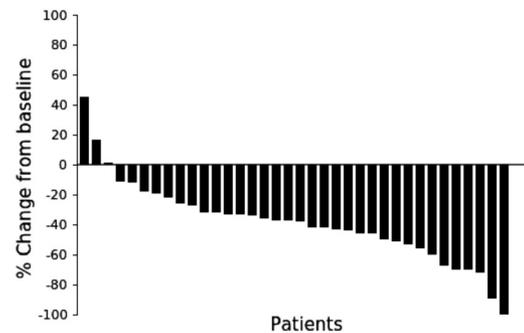


Figure 1. Waterfall plot of maximum changes in tumor size (diameter) from baseline in individual patients during the treatment.

inhibitory activity against tumor cells harboring the TKI-resistant mutation T790M [11], and is a first-line treatment for EGFR mutation-positive NSCLC [12]. The grade ≥ 3 adverse events reported in patients receiving osimertinib as a first-line treatment in the AURA study [12], AURA extension study [13], and AURA2 study [14] were rash (2%, 1%, and 1%, respectively) and diarrhea (3%, 1%, and 1%, respectively). These results suggest the possibility of relatively safe use of osimertinib with few serious adverse events for the elderly in comparison with conventional EGFR TKIs.

In the present study, which included 36 patients with EGFR T790M mutation-positive NSCLC with ineffective prior EGFR TKI treatment or with recurrence, the ORR was 58.3% (95% CI, 42.2%–72.9%), the DOR was 27.9 weeks (95% CI, 21.1–82.0), and the DCR was 97.2% with osimertinib 80 mg administration. Because the lower limit of the estimated CI exceeded a threshold of 35%, a statistically significant improvement in the ORR was demonstrated. The ORR in the present study performed in elderly patients was comparable to that in the nonelderly population [13–15]. In addition, a waterfall plot revealed that 33 (91.6%) subjects exhibited tumor shrinkage during treatment, including 12 of 14 subjects who had SD.

There were no fatal events and no adverse events that required dose reduction or discontinuation of the study drug. The results of previous findings and the present study suggest that osimertinib may be an effective and safe treatment option in elderly patients with advanced NSCLC with EGFR mutation.

TRIAL INFORMATION

Disease	Lung cancer – NSCLC
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	More than two prior regimens
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Toxicity

Additional Details of Endpoints or Study Design

Study design: This study was a single-arm, open-label trial. The rationale and design of the present study have been published elsewhere [16].

Inclusion criteria: The inclusion criteria were (a) histologically or cytologically confirmed stage IIIB–IV NSCLC and postoperative recurrence; (b) recurrence after a response better than SD or not effective (less than SD) observed in best overall response according to RECIST after treatment with EGFR TKI (e.g., erlotinib, gefitinib, afatinib) for NSCLC or (c) NSCLC harboring activating

EGFR mutations with or without T790M mutation; (d) able to accept treatment with oral medicine; (e) at least one measurable lesion according to RECIST criteria; (f) Eastern Cooperative Oncology Group (ECOG) performance status 0–1; (g) in principle, capable of participating in this study for at least A 2-week hospital stay or corresponding management; (h) ≥ 75 years of age (at the time of enrollment); (i) bone marrow, hepatic, and renal functions confirmed normal within 14 days prior to enrollment according to clinical test standards (white blood cell count $\geq 3,000/\text{mm}^3$ to $\leq 12,000/\text{mm}^3$, neutrophil count $\geq 1,500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, hemoglobin ≥ 9.0 g/dL, aspartate aminotransferase, alanine aminotransferase ≤ 100 IU/L, total bilirubin ≤ 1.5 mg/dL, creatinine ≤ 2.0 mg/dL, or SpO_2 [room air] $\geq 90\%$); (j) life expectancy of at least 3 months; (k) prior treatment having passed the planned starting point of administration (for chemotherapy, ≥ 4 weeks have passed since the final treatment of prior chemotherapy; for EGFR TKI, the next day after the last administration; for radiation therapy in the case of radiation to the chest, ≥ 12 weeks have passed since the day of final radiation treatment; for radiation therapy in the case of radiation to other than the chest, ≥ 2 weeks have passed since the day of final radiation treatment; for an operation or treatment, including chest drainage, ≥ 4 weeks have passed since the day of final operation or treatment); and (l) having provided written informed consent to participate in the study.

Exclusion criteria: The exclusion criteria were (a) treatment history of osimertinib or other third-generation EGFR TKI; (b) pulmonary disorders such as idiopathic pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, active radiation pneumonitis, and drug-induced pneumonia; (c) infectious disorders requiring intravenous injection of antibacterial drugs or antimycotics; (d) inability to swallow oral medications; (e) currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inhibitors of cytochrome P450 3A4 (CYP3A4; at least 1 week prior) or potent inducers of CYP3A4 (at least 3 weeks prior; all patients avoided concomitant use of any medications, herbal supplements, and/or ingestion of foods with known inducer or inhibitory effects on CYP3A4); (f) currently receiving checkpoint inhibitor; (g) patients with certain cardiac criteria (mean resting corrected QT interval [using Fridericia formula] >470 ms; any clinically important abnormalities in rhythm, conduction, or morphology of resting electrocardiogram [e.g., complete left-bundle branch block, third-degree heart block, second-degree heart block]; any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, unexplained sudden death under 40 years of age in first-degree relatives, or any concomitant medication known to prolong the QT interval), (h) those who are pregnant, nursing, or possibly pregnant; (i) symptomatic brain metastases; (j) active double cancer; (k) patients with uncontrollable diabetes mellitus; (l) complications of clinical concern (such as uncontrollable cardiac disease, severe cardiac arrhythmia requiring medical treatment, sustained serious diarrhea); (m) regarded as unsuitable for this study by the investigators.

Ethics: The study was conducted in accordance with ethical principles originating in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), Ethical Guidelines for Medical and Health Research Involving Human Subjects (December 22, 2014), and Ethical Guidelines for Human Genome/Gene Analysis Research (March 29, 2001). The study received ethical approval from the Ethics Committee of Kyoto Prefectural University of Medicine, Kyoto, Japan (number ERB-C-630-3, the last edition version 3, December 21, 2016). The trial was subject to the supervision and management of the Ethics Committee. All patients provided written informed consent.

Endpoints: The primary endpoint was ORR defined as the proportion of subjects whose best overall response was either CR or PR. Secondary endpoints were DCR defined as the percentage of patients who have achieved CR, PR, or SD, and safety. Depth of response (DpR), defined as maximum percent change in tumor reduction from baseline, was calculated for each subject and plotted with response status (waterfall plot). Grade and frequency of each adverse event and laboratory abnormality were recorded.

Statistical analysis: For the primary endpoint (ORR), response rate and its two-sided 95% CI were calculated using Wilson's method. When the lower limit of the estimated CI exceeded a threshold of 35%, statistical significance was decided. Disease control rate (DCR) and its 2-sided 95% CI were calculated (Wilson's method).

Investigator's Analysis

Active and should be pursued further

DRUG INFORMATION

Drug 1

Generic/Working Name	Osimertinib
Company Name	AstraZeneca
Drug Type	Small molecule
Drug Class	EGFR
Dose	Milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	Osimertinib 80 mg OD tablet was orally administered until progressive disease occurred or a criterion for discontinuation was met.

PATIENT CHARACTERISTICS

Number of Patients, Male	13
Number of Patients, Female	23
Stage	IIIB: 1, IV: 25, Postoperative recurrence: 10
Age	Median (range): 79.9 years
Number of Prior Systemic Therapies	Median (range): Not collected
Performance Status: ECOG	0 — 8 1 — 28 2 — 0 3 — 0 Unknown — 0

Other

A total of 36 patients were enrolled at 21 study centers. All 36 patients were included in the efficacy and safety analyses. Among the 36 subjects, 63.9% were female, with mean age of 79.9 years; 97.2% of the subjects had adenocarcinoma, 69.4% were at stage IV, and 27.8% had postoperative recurrent NSCLC. All patients were harboring EGFR T790M mutation: 61.1% had exon 19 deletion, and 30.6% had L858R mutation.

Cancer Types or Histologic Subtypes Adenocarcinoma, 35; Combined SCLC with adenocarcinoma, 1

PRIMARY ASSESSMENT METHOD

Title	ORR
Number of Patients Enrolled	36
Number of Patients Evaluable for Toxicity	36
Number of Patients Evaluated for Efficacy	36
Evaluation Method	RECIST 1.1
Response Assessment CR	<i>n</i> = 1
Response Assessment PR	<i>n</i> = 20
Response Assessment SD	<i>n</i> = 14
Response Assessment PD	<i>n</i> = 1
Response Assessment OTHER	<i>n</i> = 0

Outcome Notes

The ORR was 58.3% (95% CI, 42.2%–72.9%), demonstrating statistically significant efficacy of osimertinib (*p* = 0.0017). The median of the DOR was 27.9 weeks (95% CI, 21.1–82.0). CR and PR were 2.8% and 55.6%, respectively. DCR was 97.2%. The waterfall plot shows that 33 (91.6%) subjects exhibited tumor shrinkage during treatment, including 12 of 14 subjects who had SD. DpR ≥50% was achieved in 11 (30.5%) subjects and ≥30% in 26 (72.2%) subjects.

ADVERSE EVENTS**All Cycles**

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades
Fatigue	60	25	6	6	3	0	40
Rash acneiform	66	28	6	0	0	0	34
Pruritus	77	17	6	0	0	0	23
Anorexia	60	14	14	6	6	0	40
Diarrhea	63	31	3	3	0	0	37
Mucositis oral	88	6	6	0	0	0	12
Nausea	88	6	6	0	0	0	12
Pneumonitis	91	3	0	6	0	0	9
Electrocardiogram QT corrected interval prolonged	97	0	0	3	0	0	3

Pain in extremity	97	0	0	3	0	0	3
Left ventricular systolic dysfunction	97	0	0	3	0	0	3
Aspiration	97	0	0	3	0	0	3
Sinusitis	97	0	0	3	0	0	3
Fever	89	8	3	0	0	0	11
Dyspepsia	97	0	0	3	0	0	3
White blood cell decreased	60	17	17	3	3	0	40
Neutrophil count decreased	55	25	14	3	3	0	45
Platelet count decreased	52	39	6	0	3	0	48
Anemia	30	39	28	3	0	0	70
Hypoalbuminemia	28	44	25	3	0	0	72
Aspartate aminotransferase increased	58	33	3	3	3	0	42
Alanine aminotransferase increased	63	28	3	6	0	0	37
Alkaline phosphatase increased	66	31	3	0	0	0	34
Blood bilirubin increased	92	8	0	0	0	0	8
Creatinine increased	75	22	3	0	0	0	25
Paronychia	67	25	8	0	0	0	33

Abbreviation: NC/NA, No change from baseline/no adverse event.

Adverse Events Legend

Adverse events reported in 10% or more cases were fatigue (38.9%), decreased appetite (38.9%), diarrhea (36.1%), rash (33.3%), paronychia (33.3%), pruritus (22.2%), oral mucositis (11.1%), nausea (11.1%), and fever (11.1%).

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study completed

Investigator's Assessment

Active and should be pursued further

To the authors' knowledge, this is the first prospective study to examine the efficacy and safety of osimertinib in elderly patients with epidermal growth factor receptor (EGFR) mutation T790M-positive non-small-cell lung cancer (NSCLC) with disease progression on prior treatment. In the AURA phase II extension study performed in patients with EGFR mutation T790M-positive advanced NSCLC and progression after EGFR tyrosine kinase inhibitor (TKI) treatment [13], the objective response rate (ORR) was 62% (95% confidence interval [CI], 54%–68%), and in the AURA 2 phase II and AURA 3 phase III studies in patients after NSCLC progression on frontline EGFR TKI, ORR was 51%–71% [14, 15]. In comparison, the ORR of docetaxel, which is the standard treatment for elderly patients in Japanese guidelines, has been reported to be 22.7% in a controlled study with vinorelbine and 41.2% in a study of combined carboplatin and pemetrexed in elderly Japanese patients [17, 18]. Based on these findings, the expected response rate and threshold response rate are estimated to be 60% and 35%, respectively. Assuming a two-sided significance level of 5% and a power of 80%, 31 subjects were required. Considering dropouts, 35 subjects were to be enrolled in the study. In the present study, ORR was 58.3% (95% CI,

42.2%–72.9%), duration of response was 27.9 weeks (95% CI, 21.1–82.0), and the disease control rate was 97.2% with osimertinib 80 mg administration in 36 elderly subjects with EGFR T790M-positive NSCLC. Because the lower limit of the estimated CI exceeded a threshold of 35%, statistically significant improvement in the ORR was demonstrated. The ORR in the present study performed in elderly patients was comparable to those in the nonelderly population. In addition, waterfall plot revealed that 33 (91.6%) subjects exhibited tumor shrinkage during treatment, including 12 of 14 subjects who had stable disease.

The most common side effects observed in the AURA phases I–II and AURA 2 studies were gastrointestinal symptoms (diarrhea, 47%; nausea, 22%; and decreased appetite, 21%), followed by dermatologic side effects (rash, 40%; dry skin; and pruritus), and a fatal event was reported as being possibly drug-related. Hyperglycemia and QT prolongation were seen in 2% and 4%, respectively, which required no dose reduction [19]. In the present study, as for the gastrointestinal symptoms, decreased appetite was observed in more patients compared with those in the AURA studies (38.9% vs. 21%); however, diarrhea (36.1% vs. 47%) and nausea (11.1% vs. 22%) were less frequent. Among these,

grade ≥ 3 events were decreased appetite (11.1%) and diarrhea (2.8%). The most frequent dermatological symptom, rash, was less frequent in the present study versus that of the AURA studies (33.3% vs. 40%), followed by paronychia in 33.3%, but neither of these was grade ≥ 3 . There were no fatal events and no adverse events that required dose reduction or discontinuation of the study drug.

A recently conducted retrospective study compared the frequency of adverse events associated with osimertinib between elderly (aged ≥ 75 years) and nonelderly (aged < 75 years) patients with advanced NSCLC with EGFR T790M mutation [20]. Comparison was also performed between the initial EGFR TKI treatment before osimertinib administration in the same patient cohort. The results showed that the only grade ≥ 2 event that was significantly more frequent in the elderly group compared with the nonelderly group was paronychia (16.6% vs. 1.6%; $p = .04$), and the maximum grade of EGFR TKI-related adverse events associated with osimertinib in the elderly group was significantly lower than that of the initial EGFR TKI treatment ($p = .03$).

To obtain conclusive results, further studies in a larger elderly population is warranted.

Taking together the results of previous findings and the present study, osimertinib appears to be an effective and safe treatment option in elderly patients with advanced NSCLC with EGFR mutation.

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DISCLOSURES

Junji Uchino: AstraZeneca, Eli Lilly Japan K.K. (RF); **Minoru Fukuda:** AstraZeneca (H, RF); **Masaki Fujita:** AstraZeneca (H); **Koichi Takayama:** Chugai-Roche Co., Ono Pharmaceutical Co. (RF), AstraZeneca, Chugai-Roche Co., MSD-Merck Co., Eli Lilly Co., Boehringer-Ingelheim Co., DaiichiSankyo Co. (H); **Kenichi Yoshimura:** AstraZeneca, Chugai (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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FIGURE

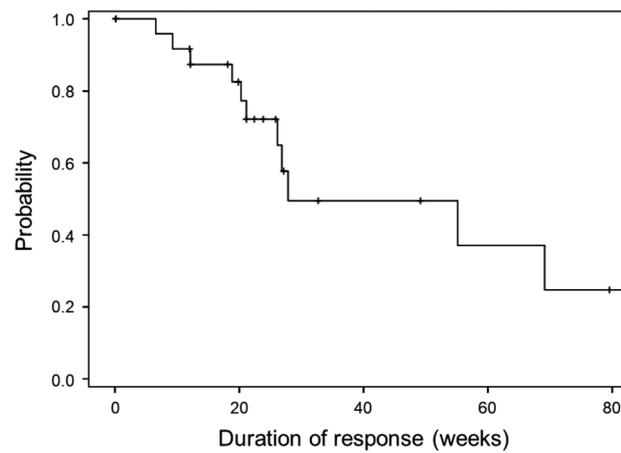


Figure 2. Kaplan-Meier curve shows the duration of response, defined as the time from the achievement of a response to progression, among 26 responders. The median of the duration of response was 27.9 weeks (95% confidence interval, 21.1–82.0 weeks).

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