CANCER DIAGNOSIS & PROGNOSIS
3: 215-220 (2023) doi: 10.21873/cdp.10204

NSCLC Patients Achieving Long-term Progression-free Survival With Docetaxel Plus Ramucirumab: A Retrospective Study

KUNIHIKO MIYAZAKI[1], TOSHIHIRO SHIOZAWA[2], SHINICHIRO OKAUCHI[3], HIROFUMI SAKURAI[2], HIROAKI SATOH[3] and NOBUYUKI HIZAWA[2]

[1]*Division of Respiratory Medicine, Ryugasaki Saiseikai Hospital, Ryugasaki, Japan;*
[2]*Division of Respiratory Medicine, Faculty of Clinical Medicine, University of Tsukuba, Tsukuba, Japan;*
[3]*Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Mito, Japan*

Abstract. *Background/Aim: The antineoplastic drug docetaxel (DOC) and the antivascular endothelial growth factor inhibitor ramucirumab (RAM) are widely used in combination for second or later-line regimens for advanced non-small cell lung cancer (NSCLC). While the median progression-free survival (PFS) of DOC+RAM has been reported to be less than six months in both clinical trials and clinical practice, there appear to be some patients with long-term PFS. This study aimed to clarify the existence and characteristics of these patients. Patients and Methods: We conducted a retrospective review of patients with advanced NSCLC treated with DOC+RAM between April 2009 and June 2022 at our three hospitals. There was no established definition of long-term PFS, thus in this study, a PFS of 12 months or longer was defined as long-term PFS. Results: During the study period, 91 patients received DOC+RAM treatment. Of these, 14 (15.4%) achieved long-term PFS. There were no significant differences in patient characteristics between patients with PFS ≥12 months and those with PFS <12 months, except for 'clinical stage IIIA-C' at DOC+RAM initiation and 'post-surgical recurrence'. In uni- and multivariate analyses, favorable factors for PFS were 'Stage III at the start of DOC+RAM' in driver gene-negative patients, and 'under 70 years old' in driver gene-positive patients. Conclusion: Many patients in this study achieved long-term PFS with DOC+RAM treatment. In the future, it is expected that long-term PFS will be defined, and the background of patients who achieve such PFS will become clearer.*

Docetaxel (DOC) is an antitumor drug that inhibits cancer cell proliferation by stabilizing microtubules, which are one of the cellular components required for cell division. Ramucirumab (RAM) is an antivascular endothelial growth factor receptor-2 (anti-VEGFR2) monoclonal antibody (1). RAM suppresses tumor growth by preventing VEGF from binding to VEGFR2 and sending downstream angiogenic signals (1). At present, combination therapy with DOC+RAM is one of the recommended second or later-line chemotherapy regimens for advanced non-small cell lung cancer (NSCLC) (2). This chemotherapy regimen is associated with high rates of myelosuppression, peripheral neuropathy, febrile neutropenia, and alopecia, which are difficult to manage (3, 4). This regimen has been confirmed to have a certain degree of efficacy in clinical trials; however, it is evaluated as of one of the standard second or later-line treatment regimens for NSCLC (5-8). Despite these evaluations, the median progression-free survival (PFS) achieved following this treatment regimen is reported to be 4.0-5.2 months in clinical trials (5, 6), and 4.3-5.8 months in clinical practice (7, 8). Indeed, NSCLC patients with long-term PFS have rarely been reported (9). In our many years of practice, though very rare, there have been some patients with long-term responses to this treatment. Therefore, we conducted a retrospective study to clarify: 1) the percentage of patients with long-term responses, and 2) the characteristics of patients who have long-term responses. We also investigated favorable factors for PFS with DOC+RAM therapy. It was hypothesized that such factors differ depending on the presence or absence of driver mutations. In addition to investigating driver mutation-negative patients,

Correspondence to: Hiroaki Satoh, MD, Ph.D., Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, 3100015, Mito, Ibaraki, Japan. Tel: +81 292312371, Fax: +81 292215137, e-mail: hirosato@md.tsukuba.ac.jp

Key Words: Non-small cell lung cancer, long-term, progression-free survival, docetaxel, ramucirumab.

Table I. *Clinicopathological features in patients who had progression-free survival of 12 months or longer.*

Patient	Age	Sex	PS	Histology	Clinical stage*	TTF-1	PD-L1	EGFR	Post-surgical relapse	Treatment line of DOC+RAM	PFS (mo)	Adverse events
1	67	M	1	AD	3B	Negative	100%		No	3	61	Edema (Grade 3)
2	86	M	1	AD	3B	Positive	24%	Ex19 del	Yes	2	29	
3	69	M	1	AD	4B	Weak, focal positive	35%		No	4	26	
4	71	F	1	SQ	3C	Negative	75%		No	2	21	
5	68	M	1	SQ	3B	Not evaluated	0		Yes	2	19	
6	50	M	1	SQ	3B	Negative	0		Yes	2	19	Stomatitis (Grade 3)
7	65	M	1	SQ	3B	Negative	60%		Yes	2	18	
8	75	F	1	AD	4A	Not evaluated	Not evaluated	Ex19 del	No	5	17	
9	65	F	1	ADSQ	4B	Not evaluated	0	Ex19 del	Yes	2	16	
10	55	M	1	AD	3B	Positive	0		No	4	15	
11	59	M	1	AD	4B	Not evaluated	Not evaluated		No	3	14	
12	62	M	1	AD	3B	Positive	0		Yes	5	13	
13	24	F	1	AD	4A	Positive	0		No	2	12	
14	79	F	1	AD	4B	Not evaluated	0	Ex21 L858R	No	2	12	

PS: Performance status; TTF-1: thyroid transcription-1; PD-L1: programmed cell death 1- ligand 1; EGFR: epidermal growth factor receptor; DOC: docetaxel; RAM: ramucirumab; PFS: progression-free survival; M: male; F: female; AD: adenocarcinoma; SQ: squamous cell cancer; ADSQ: adenosquamous cell cancer. *Clinical stage at the time of DOC+RAM initiation.

we also examined driver mutation-positive patients, a factor that has rarely been investigated (10, 11).

Patients and Methods

Patients. We examined the medical records of all patients diagnosed with NSCLC and included all the patients who were treated with DOC+RAM for any treatment line between April 2009 and June 2022 at three tertiary hospitals in Japan (Mito Medical Center, University of Tsukuba-Mito Kyodo General Hospital, and Ryugasaki Saiseikai Hospital). NSCLC was diagnosed using the World Health Organization classification. Clinical staging was determined with tumor node metastasis staging (TNM Classification, eighth edition) (12) prior to the initiation of any anticancer therapy using computed tomography/magnetic resonance imaging of the head, ultrasonography/computed tomography of the abdomen, and bone scans. The driver mutations examined were epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements. Patient demographics extracted from medical records included age, sex, Eastern Cooperative Oncology Group score for performance status, histopathology, disease stage, programmed death-ligand 1 expression, objective tumor response and survival. Tumor response was categorized as complete response, partial response, stable disease, or progressive disease, as per the Response Evaluation Criteria in Solid Tumors (version 1.1) (13). Adverse events were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) (14).

Definition of long-term PFS for DOC+RAM. There has been no established definition for 'long-term PFS' in anticancer chemotherapy, and it varies by therapy (15-18). Most of the reported 'long-term PFS' are PFS for first-line chemotherapy, and 'long-term PFS' is rarely used in second-line and subsequent treatments (19). DOC+RAM have usually been given as second or later-line chemotherapy. We searched for 'long-term PFS' for this regimen, but to our knowledge, there have been no reports to date. Therefore, we determined 'long-term PFS' by referring to the PFS of clinical trials and routine clinical practice. Median PFS in clinical trials and clinical practice was less than six months (5, 6). Based on these results (5, 6), PFS of 12 months or longer was defined as 'long-term PFS' in this study.

Statistical analysis. Nominal variables were compared using a chi-squared test and values with an unknown population variance were compared using a nonparametric Mann-Whitney test. PFS, commonly used in cancer treatment, is defined as the length of time during and after disease treatment that a patient lives with the disease but it does not get worse. PFS was calculated with a Kaplan-Meier analysis and compared using a log-rank test. Cox proportional hazards modeling with the forward-backward stepwise method was used to identify the independent variables to be included in the final model, with PFS as the dependent variable. Multivariate analyses included only variables with a p-value of less than 0.2 in univariate

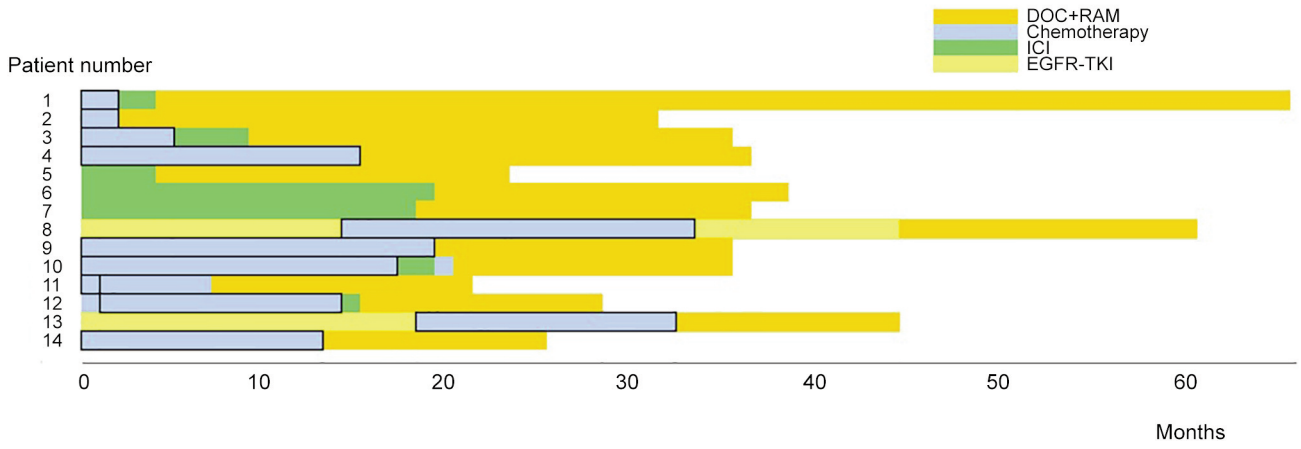

Figure 1. *The specific treatment sequences for the 14 patients who had progression-free survival of ≥12 months are shown. Bold boxes indicate pemetrexed±bevacizumab treatment. DOC: Docetaxel; RAM: ramucirumab; ICI: immune checkpoint inhibitor; EGFR-TKI: endothelial growth factor receptor-tyrosine kinase inhibitor.*

Table II. *MAPK7 gene rs2233072 (T>G) variant analysis.*

	Patients		
	Patients with PFS ≥12 months	Patients with PFS <12 months	*p*-Value
Number of patients	14	77	
Sex male:female	9:5	61:16	0.299
Age, median (range), years	67 (24-86)	66 (29-83)	0.974
PS, 0-1:2-3	14:0	77:0	0.999
Pathology, AD:others	9:5	54:23	0.755
Stage, IIIA-C:IVA-B	8:6	15:62	0.006
Relapse after resection, no:yes	6:8	9:68	0.010
EGFR, positive:negative	4:10	19:58	0.746
ALK, positive:negative	0:14	0:77	0.999
DOC+RAM, 2nd line:later lines	8:6	42:35	0.999
DOC+RAM, 2nd-3rd line:later lines	10:4	64:13	0.288

PS: Performance status; AD: adenocarcinoma; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; DOC: decetaxel; RAM: ramucirumab.

analysis. All statistical analyses were conducted using SPSS version 23 (IBM Corporation, Armonk, NY, USA). A *p*-value of less than 0.05 was considered significant.

Ethics. This study complied with the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent to participate in a non-interventional retrospective study was obtained from each patient. The Mito Medical Center-University of Tsukuba Hospital Ethics Committee approved the examination of medical records for the purpose of this study (no. 20-57).

Results

Characteristics of patients. A total of 1718 NSCLC patients were diagnosed at our three hospitals during the study period. Among them, 91 received DOC+RAM therapy. Of these 91 patients, 68 were driver gene-negative and 23 were positive. All driver gene-positive patients carried *EGFR* gene variants. The median PFS for these 91 patients was 3.0 months (range=1.0-61.0 months). Fourteen of these 91 patients (15.4%) had PFS ≥12 months. The background characteristics of these 14 patients are shown in Table I. Figure 1 shows the specific treatment sequences for these 14 patients. Two *EGFR* gene-positive patients (8.7%) and 12 driver gene-negative patients (17.6%) had PFS ≥12 months. Eleven of the 14 patients with PFS ≥12 months received pemetrexed±bevacizumab prior to DOC+RAM treatment, and seven of these had PFS ≥12 months on this treatment as well.

Table II shows the characteristics of patients with PFS <12 months and ≥12 months. The 14 patients with long-term PFS

Table III. *Uni- and multivariate analysis of survival from the initiation of docetaxel and ramucirumab in 68 driver gene-negative patients.*

	Univariate analysis (*p*-value)	Multivariate analysis		
		Odds ratio	95%CI	*p*-Value
Age, less than 70 years	0.424			
Sex, female	0.530			
Stage, IIIA-C	0.003	1.906	1.108-3.277	0.020
Pathology, AD	0.949			
Relapse, after surgical resection	0.011	1.758	0.973-3.175	0.062
DOC+RAM, 2nd to 3rd line	0.708			

EGFR: Epidermal growth factor receptor; CI: confidence interval; AD: adenocarcinoma; DOC: docetaxel; RAM: ramucirumab.

Table IV. *Uni- and multivariate analysis of survival from the initiation of docetaxel and ramucirumab in 23 patients with EGFR mutation.*

	Univariate analysis (*p*-value)	Multivariate analysis		
		Odds ratio	95%CI	*p*-Value
Age, less than 70 years	0.026	1.111	0.402-0.863	0.035
Sex, female	0.696			
Stage, IIIA-C	0.217			
Pathology, AD	0.380			
Relapse, after surgical resection	0.042	–1.336	–15.37 - –3.18	0,052
DOC plus RAM, second line	0.074			

EGFR: Epidermal growth factor receptor; CI: confidence interval; AD: adenocarcinoma; DOC: docetaxel; RAM: ramucirumab.

had a performance status of 1 at the start of DOC+RAM treatment, and there were no specific characteristic findings for age, sex, or histology in these patients, except for 'clinical stage IIIA-C' at the time of DOC+RAM initiation and 'post-surgical recurrence'. Four of the 14 patients with PFS ≥12 were *EGFR* mutation-positive.

Favorable factors for long-term PFS in 68 driver gene-negative patients. Univariate and multivariate analyses were performed to clarify favorable PFS factors, and the results are shown in Table III. In univariate analysis, 'clinical stage IIIA-C' at the time of DOC+RAM initiation and 'post-surgical recurrence' were significantly favorable factors for PFS. In multivariate analysis, only 'clinical stage IIIA-C' at the time of DOC+RAM initiation was a significantly favorable factor for PFS.

Favorable factors for long-term PFS in 23 EGFR-mutated patients. Univariate and multivariate analyses were performed to clarify favorable PFS factors, and the results are shown in Table IV. In univariate analysis, 'age less than 70 years' and 'post-surgical recurrence' were significantly favorable factors for PFS at the start of DOC+RAM treatment. In multivariate analysis, only 'age less than 70 years' was a significantly favorable factor for PFS.

Discussion

In the present study, we revealed that there was a small proportion of NSCLC patients with PFS >12 months on DOC+RAM therapy. 'Clinical stage IIIA-C' at the time of DOC+RAM initiation and 'post-surgical recurrence' were identified as characteristics of patients with such long-term PFS. In uni- and multivariate analyses of all patients treated with DOC+RAM, 'clinical stage IIIA-C' at the time of DOC+RAM initiation was a favorable factor in driver gene-negative patients. On the other hand, among driver gene-positive patients, all of whom carried the *EGFR* mutation, 'age less than 70 years' was a favorable factor.

DOC+RAM therapy has been evaluated as one of the standard treatments for second or later-line therapy for patients with advanced NSCLC (5-8). Although there have been reports of patients with long-term responses to DOC without RAM (20, 21), combination with RAM has been shown to extend the duration of response (5-8).

DOC+RAM has been evaluated as a second or later-line therapy, and the median PFS with DOC+RAM has been reported to be less than six months in both clinical trials and clinical practice (5-8). Although there have been few reports of patients with long-term responses to DOC+RAM (9), we occasionally encounter patients with long-term response in

routine clinical practice. Therefore, this research was conducted with the aim of clarifying the ratio and characteristics of such patients. Although we were unable to clarify patient characteristics associated with long-term PFS, we were able to show that there were a number of such patients. As far as we could determine, this is the first study with such a relatively large number of patients, and so there are no previous studies with which to compare. In the future, it is expected that more investigations will be conducted into the long-term response to DOC+RAM treatment. In this sense, our report provides valuable data for later comparison.

It is difficult to clearly explain the underlying reasons behind the favorable factors for PFS obtained in this study. It is possible that the increased PFS in driver gene-negative patients with stage III disease at the time of recurrence could indicate the relationship between small tumor burden and reduced spread of lesions. All patients studied were regularly monitored for recurrence after first-line therapy. In other words, patients remained in stage III disease, with relatively low tumor burden and without distant metastases. We hypothesized that patients with these characteristics might have been associated with longer PFS than those without. Similarly, it is difficult to explain why '70 years or younger' was a favorable factor for PFS in driver gene-positive patients, as it is known that *EGFR* gene mutation impacts a higher proportion of young patients (18, 19). As DOC side effects are known to be painful, it is possible that younger patients may have tolerated these side effects and remained on treatment longer than older patients.

Of the 14 patients with long-term PFS, one had grade 3 edema and one had grade 3 stomatitis. Interestingly, the patient with edema discontinued DOC+RAM therapy but had a long-term follow-up without recurrence on periodic imaging evaluations. Of these 14 patients with PFS of 12 months or longer, three patients received first-line therapy that included immune checkpoint inhibitors. Due to this small number of patients, it was not possible to analyze these patients separately. In the future, the positioning of DOC+RAM therapy after treatment including immune checkpoint inhibitors should also be evaluated.

In addition to the above point, our present study has some limitations. Although data from patients across three institutions were examined, this was a retrospective study with a relatively small number of patients with variable background characteristics. It should be noted that the results are provisional and did not provide a final, statistically valid conclusion. *EGFR* mutation and *ALK* rearrangements were examined as driver genes in all patients, however, tests for additional driver genes were performed in a subset of patients as they became newly available during the study period. In addition, there were no patients carrying the ALK rearrangement, and, as a result, all the driver gene-positive patients were *EGFR*-positive patients. For driver gene-positive patients, a detailed examination of the response to DOC+RAM therapy for each driver gene will be necessary in the future.

There is no established definition of long-term response to therapy. In this study, the long-term response was defined as having PFS of 12 months or longer. Under this definition, this study revealed that there is a certain number of patients with long-term PFS. Moving forward, a commonly accepted definition of long-term PFS should be established. It is also expected that characteristics common to patients with long-term PFS will be clarified.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

KM, TS, SO, HSaku and HS designed the study. KM, TS, SO and HS collected the data. KM, SO and HS analyzed the data. KM, SO, HS and NH prepared the manuscript. HS and NH supervised the study. All Authors approved the final version for submission.

References

1 Janning M and Loges S: Anti-angiogenics: their value in lung cancer therapy. Oncol Res Treat *41(4)*: 172-180, 2018. PMID: 29631257. DOI: 10.1159/000488119

2 Alshangiti A, Chandhoke G and Ellis PM: Antiangiogenic therapies in non-small-cell lung cancer. Curr Oncol *25(Suppl 1)*: S45-S58, 2018. PMID: 29910647. DOI: 10.3747/co.25.3747

3 Okeya K, Kawagishi Y, Yamoto M, Shimizu M, Imizuda T and Tsuji H: Interstitial lung disease induced by docetaxel and ramucirumab chemotherapy after nivolumab treatment. Respirol Case Rep *8(5)*: e00564, 2020. PMID: 32337046. DOI: 10.1002/rcr2.564

4 Cobo M, Gutiérrez V, Villatoro R, Trigo JM, Ramos I, López O, Ruiz M, Godoy A, López I and Arroyo M: Spotlight on ramucirumab in the treatment of nonsmall cell lung cancer: design, development, and clinical activity. Lung Cancer (Auckl) *8*: 57-66, 2017. PMID: 28744168. DOI: 10.2147/LCTT.S118996

5 Reck M, Paz-Ares L, Bidoli P, Cappuzzo F, Dakhil S, Moro-Sibilot D, Borghaei H, Johnson M, Jotte R, Pennell NA, Shepherd FA, Tsao A, Thomas M, Carter GC, Chan-Diehl F, Alexandris E, Lee P, Zimmermann A, Sashegyi A and Pérol M: Outcomes in patients with aggressive or refractory disease from REVEL: A randomized phase III study of docetaxel with ramucirumab or placebo for second-line treatment of stage IV non-small-cell lung cancer. Lung Cancer *112*: 181-187, 2017. PMID: 29191593. DOI: 10.1016/j.lungcan.2017.07.038

6 Yoh K, Hosomi Y, Kasahara K, Yamada K, Takahashi T, Yamamoto N, Nishio M, Ohe Y, Koue T, Nakamura T, Enatsu S, Lee P, Ferry D, Tamura T and Nakagawa K: A randomized, double-blind, phase II study of ramucirumab plus docetaxel *vs.* placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy. Lung Cancer *99*: 186-193, 2016. PMID: 27565938. DOI: 10.1016/j.lungcan.2016.07.019

7 Kawachi H, Tamiya M, Matsumoto K, Tamiya A, Yanase T, Tanizaki S and Kumagai T: Efficacy and safety of ramucirumab and docetaxel in previously treated patients with squamous cell lung cancer: a multicenter retrospective cohort study. Invest New Drugs *40(3)*: 634-642, 2022. PMID: 35024985. DOI: 10.1007/s10637-022-01214-w

8 Matsumoto K, Tamiya A, Matsuda Y, Taniguchi Y, Atagi S, Kawachi H, Tamiya M, Tanizaki S, Uchida J, Ueno K, Yanase T, Suzuki H and Hirashima T: Impact of docetaxel plus ramucirumab on metastatic site in previously treated patients with non-small cell lung cancer: a multicenter retrospective study. Transl Lung Cancer Res *10(4)*: 1642-1652, 2021. PMID: 34012781. DOI: 10.21037/tlcr-20-1263

9 Kamiyoshihara M, Yazawa T, Igai H, Matsuura N, Ohsawa F and Iwashita H: [Docetaxel and Ramucirumab Combination Chemotherapy after Nivolumab Treatment for Pretreated Pulmonary Squamous Cell Carcinoma-A Successful Case]. Gan To Kagaku Ryoho *48(2)*: 211-213, 2021. PMID: 33597361.

10 Ellis-Caleo T and Neal JW: The role of ramucirumab with docetaxel in epidermal growth factor receptor mutant and wild-type non-small cell lung cancer. J Thorac Dis *13(8)*: 4864-4871, 2021. PMID: 34527325. DOI: 10.21037/jtd-21-557

11 Furuya N, Ito K, Sakaguchi T, Hida N, Kakinuma K, Morikawa K, Inoue T, Komase Y, Hataji O and Mineshita M: The impact of EGFR mutation status and brain metastasis for non-small cell lung cancer treated with ramucirumab plus docetaxel. Oncology *98(9)*: 661-668, 2020. PMID: 32464632. DOI: 10.1159/000507050

12 Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V, International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions and International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions: The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol *11(1)*: 39-51, 2016. PMID: 26762738. DOI: 10.1016/j.jtho.2015.09.009

13 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

14 National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Available at: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fctep.cancer.gov%2FprotocolDevelopment%2Felectronic_applications%2Fdocs%2FCTCAE_v5.0.xlsx&wdOrigin=BROWSELINK [Last accessed on December 20, 2022]

15 Sumodhee S, Bondiau PY, Poudenx M, Cohen C, Naghavi AO, Padovani B, Maneval D, Gal J, Leysalle A, Ghalloussi H, Otto J and Doyen J: Long term efficacy and toxicity after stereotactic ablative reirradiation in locally relapsed stage III non-small cell lung cancer. BMC Cancer *19(1)*: 305, 2019. PMID: 30943943. DOI: 10.1186/s12885-019-5542-3

16 Drilon A, Chiu CH, Fan Y, Cho BC, Lu S, Ahn MJ, Krebs MG, Liu SV, John T, Otterson GA, Tan DSW, Patil T, Dziadziuszko R, Massarelli E, Seto T, Doebele RC, Pitcher B, Kurtsikidze N, Heinzmann S and Siena S: Long-term efficacy and safety of entrectinib in ROS1 fusion-positive NSCLC. JTO Clin Res Rep *3(6)*: 100332, 2022. PMID: 35663414. DOI: 10.1016/j.jtocrr.2022.100332

17 Chu X, Niu L, Xiao G, Peng H, Deng F, Liu Z, Wu H, Yang L, Tan Z, Li Z and Zhou R: The long-term and short-term efficacy of immunotherapy in non-small cell lung cancer patients with brain metastases: a systematic review and meta-analysis. Front Immunol *13*: 875488, 2022. PMID: 35693805. DOI: 10.3389/fimmu.2022.875488

18 Gettinger SN, Huber RM, Kim DW, Bazhenova L, Hansen KH, Tiseo M, Langer CJ, Paz-Ares Rodríguez LG, West HL, Reckamp KL, Weiss GJ, Smit EF, Hochmair MJ, Kim SW, Ahn MJ, Kim ES, Groen HJM, Pye J, Liu Y, Zhang P, Vranceanu F and Camidge DR: Long-term efficacy and safety of brigatinib in crizotinib-refractory ALK+ NSCLC: Final results of the phase 1/2 and randomized phase 2 (ALTA) trials. JTO Clin Res Rep *3(9)*: 100385, 2022. PMID: 36065449. DOI: 10.1016/j.jtocrr.2022.100385

19 Igawa S, Yokoba M, Takakura A, Hosotani S, Nakahara Y, Sato T, Mitsufuji H, Sasaki J and Naoki K: Real-world evaluation of second line chemotherapy for patients with advanced non-small cell lung cancer harboring preexisting interstitial lung disease. Invest New Drugs *40(1)*: 182-189, 2022. PMID: 34415485. DOI: 10.1007/s10637-021-01162-x

20 Andritzky B, Schuch G, Thoem I, Goern M, Brandl S, Bokemeyer C and Laack E: Long-term survival after second-line therapy with docetaxel and carboplatin and monthly pamidronic acid in a woman with metastatic non-small cell lung cancer. Onkologie *29(5)*: 206-208, 2006. PMID: 16679782. DOI: 10.1159/000092263

21 Matsuzaki T, Iwami E, Sasahara K, Kuroda A, Nakajima T and Terashima T: A case report of metastatic lung adenocarcinoma with long-term survival for over 11 years. Medicine (Baltimore) *98(4)*: e14100, 2019. PMID: 30681568. DOI: 10.1097/MD.0000000000014100

Received December 23, 2022
Revised December 30, 2022
Accepted January 2, 2023