BRIEF REPORT

A Phase II Study of Trastuzumab Emtansine in HER2-Positive Non–Small Cell Lung Cancer

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Received 10 September 2017; revised 26 October 2017; accepted 31 October 2017
Available online - 4 December 2017

ABSTRACT

Trastuzumab emtansine (T-DM1), an anti–erb-b2 receptor tyrosine kinase 2 (HER2) antibody-drug conjugate, has been shown to significantly improve survival in HER2-positive breast cancer. We report a phase II trial of T-DM1 monotherapy in relapsed NSCLC with documented HER2 positivity (an immunohistochemistry [IHC] score of 3+, both an IHC score of 2+ and fluorescence in situ hybridization positivity, or exon 20 mutation). This study was terminated early because of limited efficacy. The demographic characteristics in the 15 assessable patients were as follows: median age, 67 years; male sex, 47%; performance status of 0 to 1, 80%; HER2 status IHC 3+, 33%; HER status IHC 2+/fluorescence in situ hybridization–positive, 20%; and exon 20 mutation, 47%. The median number of delivered cycles was 3 (range 1–11). One patient achieved a partial response with an objective response rate of 6.7% (90% confidence interval: 0.2–32.0). With a median follow-up time of 9.2 months, the median progression-free survival time and median survival time were 2.0 and 10.9 months, respectively. Grade 3 or 4 adverse events included thrombocytopenia (40%) and hepatotoxicity (20%) without any treatment-related deaths. T-DM1 had a limited efficacy for HER2-positive NSCLC in our cohort. Applying the concept of precision medicine to tumors appears challenging; thus, additional molecular approaches are warranted.

Keywords: Non–small cell lung cancer; HER2; trastuzumab emtansine; precision medicine

Introduction

Recent driver oncogene–based precision therapy has dramatically changed the treatment strategy for NSCLC, representatively targeting *EGFR* and ALK receptor tyrosine kinase gene (*ALK*) aberrations. However, outcomes in other lung cancers remain poor even with standard chemotherapy.[1,2] Consequently, further development of novel oncogenes and corresponding targeted therapeutic agents is warranted.

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Disclosure: Dr. Hotta has received honoraria outside the current work from AstraZeneca, Ono Pharmaceutical, Astellas, Novartis, Bristol-Myers Squibb, Merck Sharp Dohme, Eli Lilly Japan, Daiichi-Sankyo Pharmaceutical, Boehringer-Ingelheim, Nihon Kayaku, Taiho Pharmaceutical, and Chugai Pharmaceutical. Dr. Hotta also has received research funding outside the current work from AstraZeneca, Boehringer-Ingelheim, Ono Pharmaceutical, Astellas, Novartis, Bristol-Myers Squib, Eli Lilly Japan, Merck Sharp Dohme, and Chugai Pharmaceutical. Dr. Ohashi has received a research grant from Novartis Pharmaceuticals Japan. Dr. Katsuyuki Kiura has received honoraria from Eli Lilly Japan, Nihon Kayaku, AstraZeneca, Daiichi-Sankyo Pharmaceutical, Chugai Pharmaceutical, Taiho Pharmaceutical, and Sanofi-Aventis. The remaining authors declare no conflict of interest.

Trial Registration: A Study of Trastuzumab Emtansine in Patients with HER2-Positive, Recurrent Metastatic Non-Small Cell Lung Cancer. UMIN000017709.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2017.10.032

In addition, erb-b2 receptor tyrosine kinase 2 (HER2) aberrations have been detected, accounting for 4.7% to 10% of NSCLC in terms of grade 3+ HER2 immunohistochemistry (IHC) expression.[3] Additionally, the large epidemiological studies have identified tumors with positive HER2 fluorescence in situ hybridization (FISH) in 1.7% and HER2-mutant tumors in 3.6%.[4]

Trastuzumab emtansine (T-DM1) is a novel antibody-drug conjugate that uses trastuzumab, an anti-HER2 antibody, to deliver the maytansinoid antimicrotubule agent DM1, which binds to microtubules in a manner similar to that of vinca alkaloids.[5] T-DM1 has been shown to confer a survival benefit over the standard regimen applied in HER2-positive, relapsed breast cancer.[6]

As for NSCLC, the Calu 3 lung carcinoma cell line (HER2-IHC 3+) showed preclinically dose-dependent inhibition of cell growth after T-DM1 treatment.[5] Moreover, lung tumors with erb-b2 receptor tyrosine kinase 2 gene (*HER2*) insertion mutations in exon 20, a confirmed driver oncogene, showed dramatic shrinkage with HER2-targeted therapy.[7] These studies suggested that T-DM1 might be effective against both HER2-positive lung and breast cancers.

However, few prospective studies of HER2-targeted therapy for lung cancer have been conducted, prompting us to launch this phase II trial.

Methods

Study Population and Intervention

Patients who met the eligibility criteria, including HER2 positivity,[8] were enrolled for registration at three institutes in Japan: Yamaguchi-Ube Medical Centre, Shikoku Cancer Centre, and Okayama University Hospital. T-DM1 was kindly provided by Chugai Pharmaceuticals. Patients had to have had one or more lines of prior chemotherapy. Written informed consent was obtained from all patients before applying the study procedures. This study was approved by the institutional review boards.

Patients received T-DM1 intravenously, at a dose of 3.6 mg/kg over 90 minutes on day 1 of each 21-day cycle until the disease progressed or unmanageable toxic effects developed, as similar to the protocol for breast cancer.[6]

HER2 Tests

HER2 status was assessed in the laboratory (SRL, Tokyo, Japan) by using tumor formalin-fixed, paraffin-embedded archived tissues; no cytologic specimens were allowed, but biopsy or surgical specimens were. The level of HER2 protein expression was determined by IHC by using the Ventana I-VIEW PATHWAY anti–HER-2/neu (4B5) (Roche, Basel, Switzerland).[9] IHC scores of 3+ and 2+ were considered strongly and weakly positive, respectively.[9] FISH assays were also performed using the PathVysion HER-2 DNA probe kit (Vysis/Abbott Laboratories, Downers Grove, IL) to ascertain negativity or positivity according to a cutoff value of 2.0 (of the median ratio of HER2 to chromosome 17 copy numbers). We conducted a separate validation study to review the IHC and FISH specimens to define their positivity (unpublished data, Hotta K, 2017). Mutation analysis was performed by direct sequencing at a central laboratory (Genetic Labo, Japan) to detect known mutations (M774_A775insAYVM, A775_G776insYVMA, G776L insC, G776V insC, and P780_Y781insGSP).[4]

Finally, in this trial, HER2 was defined as positive in the presence of an IHC score of 3+, an IHC score of 2+ and FISH positivity, or an exon 20 insertion mutation.

Statistical Analysis

The primary end point was the objective response rate (ORR), which was centrally confirmed by three independent board members with the Response Evaluation Criteria in Solid Tumors (version 1.1) every 6 weeks. Secondary outcome end points included safety, overall survival, and progression-free survival (PFS). We considered the lower limit of interest to be 10%.[10] Assuming that a 20% or more increase in historical data in ORR would be clinically meaningful, we needed 30 patients with a one-sided α of 0.05 and 1-β of 0.8, considering a 10% dropout rate, according to the Simon minimax design. We also planned to conduct an interim analysis after the first 15 patients had been registered; early study termination would be considered if the ORR was obtained in no more than one patient. The confidence interval (CI) of the ORR was calculated with a confidence coefficient of two-tailed 90% and 95%.

Regarding the efficacy analysis, waterfall and swimmer plots were also produced. The PFS and overall survival times were calculated from the date of registration to the first documented date of disease progression and date of death, respectively, by the Kaplan-Meier method. Statistical analyses were conducted with STATA software (version 14.0, StataCorp LP, College Station, TX).

Results

Patients

This study was terminated early because of the limited efficacy, which did not satisfy the criteria in the interim analysis; this led to only 16 of the 30 patients planned being registered between September 2015 and November 2016. Among them, 15 were considered assessable for further analysis: one patient was excluded because of a protocol deviation in the registration process. The patients' characteristics are listed in Table 1. Regarding HER2 status, 33% of cases were scored IHC 3+, 20% were scored IHC 2+/FISH positive, and 47% showed the

mutations. All 15 patients were followed up sufficiently to allow assessment of the primary end point.

Treatment Delivery

The treatment delivery is summarized in Table 2. The median delivered number of cycles to each patient was 3 (Table 2). Four patients (27%) required dose reduction during the second cycle or later because of adverse events (AEs) (see Table 2). Treatment was ultimately discontinued in all patients, mainly on account of disease progression (see Table 2).

ORR and Survival

A partial response was centrally confirmed in a female patient with a HER2-mutant tumor (Table 3). Thus, the ORR (the primary end point) was 6.7% (90% CI: 0.2%–32.0%, 95% CI: 0.3%–27.9%), whereas seven patients (46.7%) each had stable disease and progressive disease (Fig. 1*A*). When patients were stratified by type of HER2 aberration, no tumor shrinkage was seen in the subgroup with an IHC score of 3+ or IHC 2+/FISH-positive tumors (n = 8) (Fig. 1*B* and Table 3). With a median follow-up time of 9.2 months, the median PFS time was 2.0 months (90% CI: 1.2–4.0, 95% CI: 1.4–4.0), whereas the median survival time was 10.9 months (90% CI: 2.3–, 95% CI: 4.4–12.0) (Fig. 2*A* and *B*).

Table 1. Patient Characteristics (N = 15)

Characteristic	Value
Median age (range), y	67 (45-77)
Sex	
Male/female	7 (47%)/8 (53%)
Smoking status	
Never/ever	10 (67%)/5 (33%)
ECOG PS	
0	2 (13%)
1	10 (67%)
2	3 (20%)
Adenocarcinoma histologic type	15 (100%)
Stage IV/recurrence[a]	9 (60%)/6 (40%)
HER2 positivity	
IHC 3+	5 (33%)
IHC 2+/FISH-positive	3 (20%)
Exon 20 mutations	7 (47%)
A775_G776insYVMA	5 (33%)
P780_Y781insGSP	1 (7%)
G776VinsC	1 (7%)
Other driver oncogenes	
EGFR	2 (13%)[b]
EML4-ALK	0
Median No. of prior chemotherapy regimens (range)	4 (1-7)

[a]Postoperative recurrence.
[b]Exon 19 deletion and exon 21 point mutation in one patient each.
ECOG, Eastern Cooperative Oncology Group; PS, performance status; HER2, erb-b2 receptor tyrosine kinase 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; EML4, echinoderm microtubule-associated protein-like 4 gene; ALK, anaplastic lymphoma kinase.

Table 2. Treatment Delivery (N = 15)

Characteristic	Value
Total no. of treatment cycles, median (range)	3 (1-11)
Cycles received	
≥4 cycles	6 patients (40%)
3 cycles	2 patients (13%)
2 cycles	5 patients (33%)
1 cycle	2 patients (13%)
No. of patients with dose reduction	4 (27%)
Reasons for dose reduction	
Thrombocytopenia	2 patients
AST elevation	1 patient
Infusion reaction	1 patient
No. of patients who discontinued treatment	15 (100%)
Reasons for discontinuation of treatment	
Disease progression	12
Adverse events[a]	2
Attending doctor's discretion	1

[a]Interstitial pneumonia (grade 2) and prolonged thrombocytopenia (grade 3) in one patient each.
AST, aspartate transaminase.

Safety

All grade 3 to 4 AEs are listed in Table 4. Almost all of the AEs were known ones, primarily thrombocytopenia (n = 6 [40%]) and hepatotoxicity (n = 3 [20%]). Among the 15 patients, there was no case of treatment-related death.

Grade 3 acute renal failure with a serum creatinine level of 3.08 mg/dL developed in one patient. The AE was

Table 3. Objective Response

	CR	PR	Stable Disease	PD
Overall cohort (N = 15)	0	1 (6.7%)	7 (46.7%)	7 (46.7%)
Subgroups by HER2 aberration pattern				
IHC/FISH-positive (n = 8)	0	0	3 (37.5%)	5 (62.5%)
Mutant-positive (n = 7)	0	1 (14.3%)	4 (57.1%)	2 (28.6%)
A775_G776insYVMA (n = 5)	0	1	3	1
G776VinsC (n = 1)	0	0	0	1
P780_Y781insGSP (n = 1)	0	0	1	0

Note: The objective response rate (i.e., the primary end point) was centrally confirmed by three independent extramural review board members and evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) every 6 weeks.
CR, complete response; PR, partial response; PD, progressive disease; HER2, erb-b2 receptor tyrosine kinase 2 IHC, immunohistochemistry; FISH, fluorescence in situ hybridization.

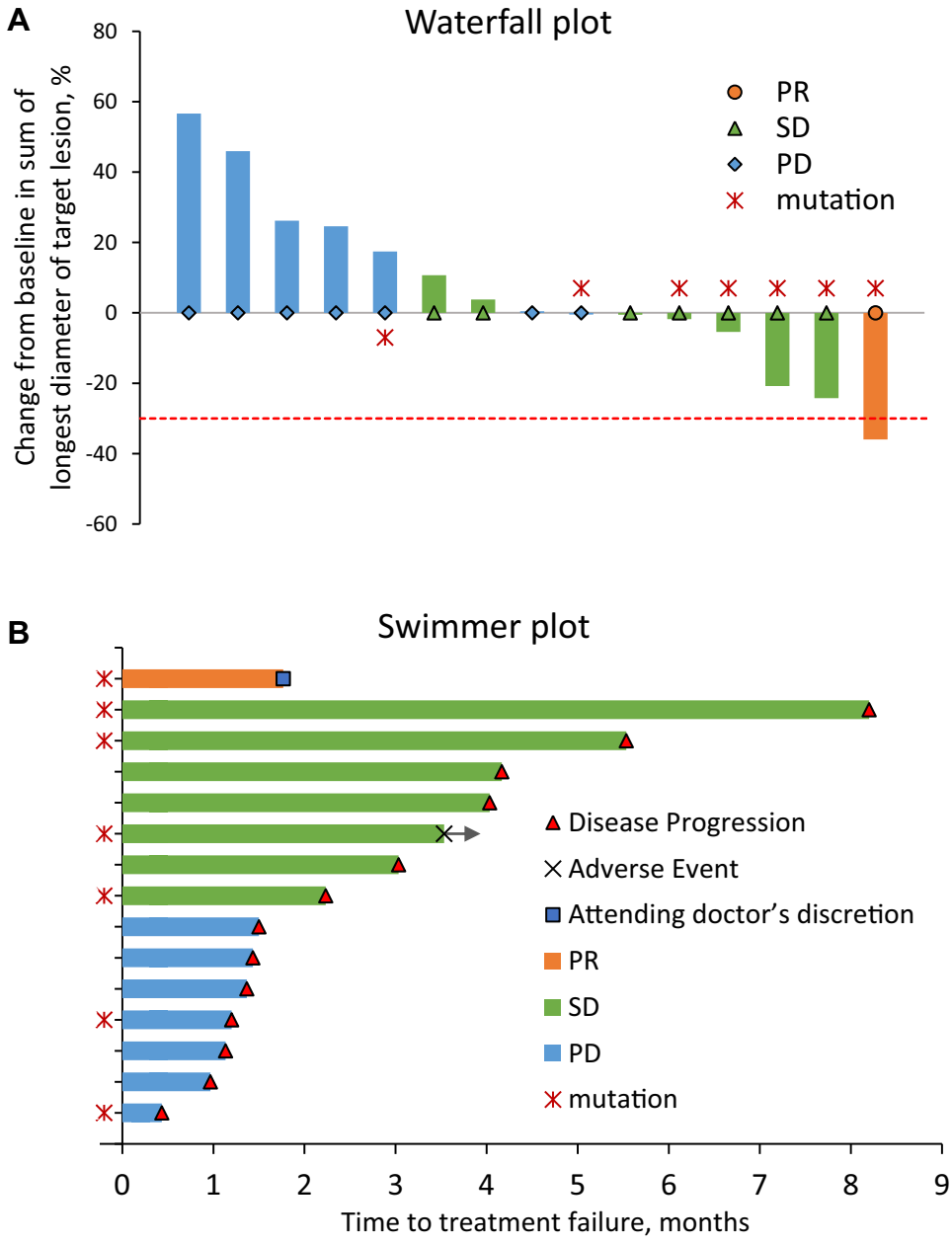

Figure 1. Objective response rate (N = 15). Waterfall plot (*A*) and swimmer plot (*B*). In the case of one responder, the attending physician judged progressive disease (PD) at an earlier time in the treatment course than did the independent radiologic review committee. PR, partial response.

recovered to grade 0 within 1 week during provision of appropriate supportive care. Interstitial pneumonia was observed in one patient (grade 2) during the fifth cycle, as detected by computed tomography. No further examination with bronchoscopy was performed in this case and the AE was resolved shortly thereafter without any steroid or oxygen therapy but just discontinuation of T-DM1.

Discussion

In this study, 1 of 15 patients (6.7%) responded to T-DM1, which did not meet the primary end point (see Table 3). The median PFS and median survival times were 2.0 and 10.9 months, respectively. The AE profiles were almost the same as those obtained in trials for approval for use in breast cancer.[6]

The investigational agent did not show high efficacy in this study (see Table 3 and Fig. 1), which is similar to the results of the very recent trials investigating HER2-targeted therapy in lung cancer (Supplementary Table 1). In particular, IHC 3+ or IHC 2+/FISH-positive tumors were rarely responsive to the investigational agent in this study (see Fig. 1 and Table 3). Although the precise reason remains unknown, it could be

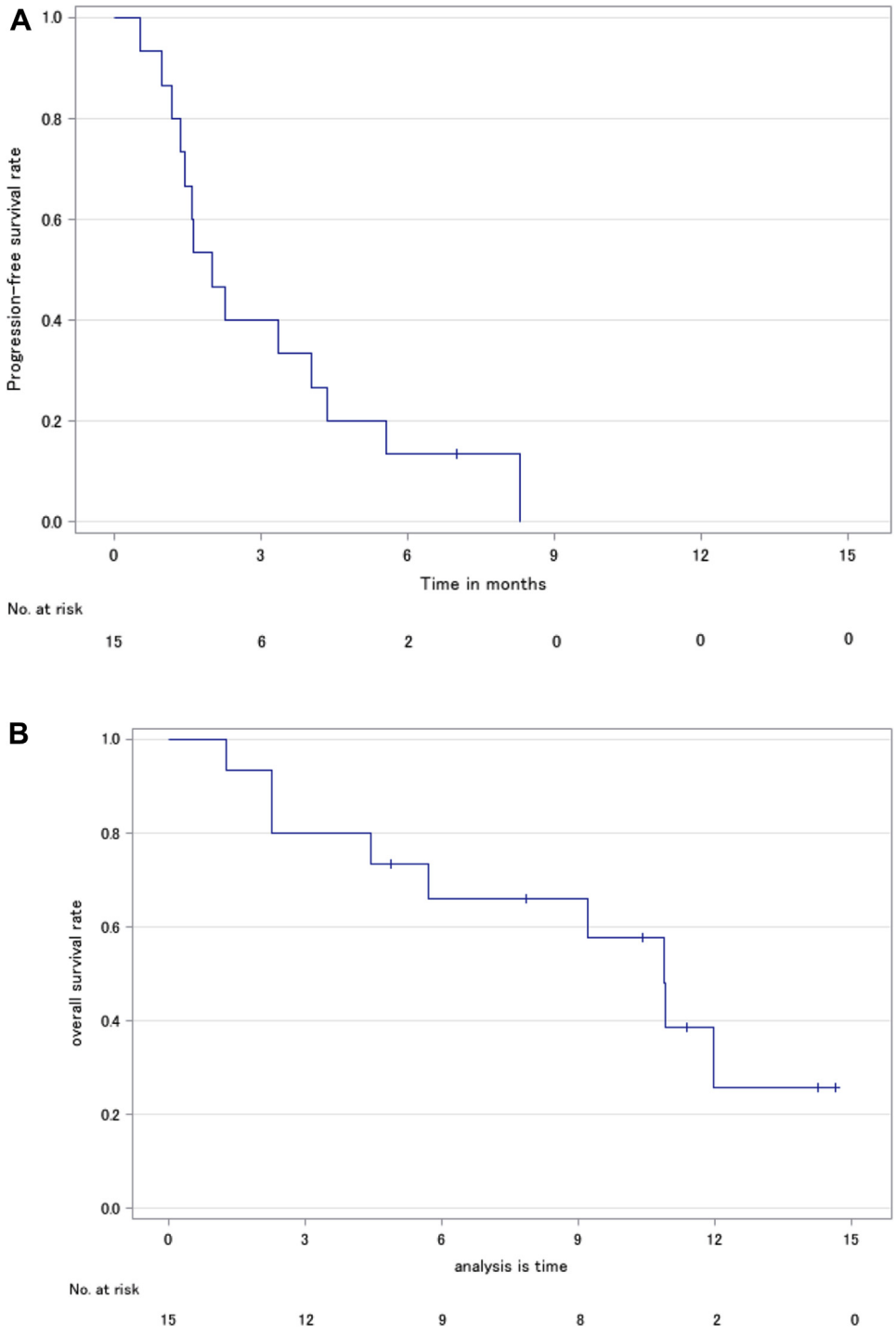

Figure 2. Survival (N = 15). Progression-free survival (*A*) and overall survival (*B*).

attributable to tumor heterogeneity, which was detected in 30% of the NSCLC cases.[11] It may be that only strongly HER2-immunostained cells were killed in the tumors after exposure to T-DM1, whereas the weakly stained cells might have escaped cell death and continued to grow. Unfortunately, we did not obtain or analyze tumor specimens at the time of disease progression. Further molecular analyses are warranted to elucidate the mechanisms underlying these tumors.

Another reason for the low sensitivity could be molecularly inappropriate patient selection. We might have overestimated HER2 IHC positivity because in the present study, we used the scoring system for IHC status that is applied to gastric cancer, which is less strict than

Table 4. Grade 3 to 4 Adverse Events

Category	Grade 3	Grade 4	Grades 3-4
Thrombocytopenia	5 (33%)	1 (7%)	6 (40%)
Hypokalemia	1 (7%)	0 (0%)	1 (7%)
Hyperuricemia	0 (0%)	1 (7%)	1 (7%)
AST/ALT level increase	1 (7%)	0 (0%)	1 (7%)
γ-GTP level increase	1 (7%)	0 (0%)	1 (7%)
LFT result abnormality	1 (7%)	0 (0%)	1 (7%)
Decreased appetite	1 (7%)	0 (0%)	1 (7%)
Nausea	1 (7%)	0 (0%)	1 (7%)
Acute renal failure	1 (7%)	0 (0%)	1 (7%)
Gingivitis	1 (7%)	0 (0%)	1 (7%)
Lung infection	1 (7%)	0 (0%)	1 (7%)

Note: No treatment-related deaths were observed.
ALT, Alanine transaminase; AST, aspartate transaminase; LFT, liver function test; γ-GTP, γ-glutamyltransferase.

that used for breast cancer.[9] Furthermore, the sensitivity of HER2-targeted agents was dependent on the IHC staining intensity.[12]

Regarding HER2-mutant tumors, we designed this study to limit the types of mutations to those confirmed as driver oncogenes in previous reports[4] but did not exclude tumors with co-mutation in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene (*PIK3CA*); such mutation was reported as a potential intrinsic resistance mechanism, possibly leading to the low sensitivity.

The current study had several limitations. First, it used a single-arm design, and various potential biases could not be eliminated. Additionally, the study comprised a small number of patients recruited from only a few institutes in one country, thus lowering the likelihood of confirmative results. The relationship between type of HER2 mutations and efficacy also remains unknown. Our study results should be interpreted together with those of relevant previous studies (see Supplementary Table 1).

In conclusion, T-DM1 showed limited efficacy against HER2-positive NSCLCs in our cohort. It seems that the concept of precision medicine is difficult to apply to tumors. Additional molecular approaches are warranted for precision medicine in the treatment of HER2-positive tumors.

Acknowledgments

This research was supported by a specific grant from the Japan Agency for Medical Research and Development, which is funded by the Japanese government. No additional external funding was received for this study. The investigational agent was kindly provided by Chugai Pharmaceuticals. All of the authors contributed to the writing of the study protocol. Kadoaki Ohashi, Katsuyuki Hotta, Taizo Hirata, Kiichiro Ninomiya, and Katsuyuki Kiura also participated in the trial design and setup. Kadoaki Ohashi, Katsuyuki Hotta, Kiichiro Ninomiya, and Katsuyuki Kiura calculated the required sample size.

Appendix

The contributing members of the HER2-CS Group are as follows:

Steering Committee: K. Hotta, K. Ohashi, K. Ninomiya, T. Hirata, S. Hinotsu, S. Toyooka, and K. Kiura.

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Independent Data and Safety Monitoring Committee: T. Kato (Kanagawa Cancer Center), J. Sasaki (Kitazato University), and N. Ebi (Iizuka Hospital).

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This study was conducted with dedicated support from the following persons:

HER2-CS Group: S. Harita, G. Ikeda, M. Yasugi, E. Kurimoto, K. Nakano, and K. Gemba (Chugoku Central Hospital); T. Moritaka and K. Inoue (Ehime Prefectural Central Hospital); S. Miyoshi, N. Hamaguchi, R. Ito, and Y. Sano (Ehime University Hospital); I. Takata and A. Mitani (Fukuyama City Hospital); N. Ishikawa, T. Nishisaka, H. Shoda, A. Nishida, K. Hamai, and S. Tamamoto (Hiroshima Prefectural Hospital); M. Yamasaki (Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital); K. Fujitaka, T. Masuda, S. Miyamoto, and N. Hattori (Hiroshima University Hospital); K. Sugimoto, S. Fujii, and Y. Ueda (Japanese Red Cross Kobe Hospital); A. Bessho, S. Hosokawa, Y. Sakugawa, N. Fukamatsu, and K. Ogata (Japanese Red Cross Okayama Hospital); T. Murakami (Japanese Red Cross Society Himeji Hospital); Y. Ueda (Kagawa Prefectural Central Hospital); S. Bandoh and N. Kanaji (Kagawa University Hospital); N. Takigawa, H. Yamane, N. Ochi, and Y. Honda (Kawasaki Hospital); M. Oka and M. Kittaka (Kawasaki Medical School Hospital); T. Kubota and A. Yokoyama (Kochi Medical School Hospital]); H. Yoshioka, T. Tanaka, T. Yokoyama, and E. Sato (Kurashiki Central Hospital); Y. Shiota and N. Horita (Kure Kyosai Hospital); T. Kanematsu (Matsuyama Red Cross

Hospital); Y. Awaya, A. Nakamasu, and Y. Sano (Miyoshi Central Hospital); I. Murakami (NHO Higashi-Hiroshima Medical Center); S. Kuyama, K. Kudo, T. Tamura, T. Umeno, and D. Morichika (NHO Iwakuni Medical Center); T. Shibayama, K. Fujiwara, and Sato K (NHO Okayama Medical Center); K. Nishii (Okayama Health Foundation Hospital); Fujimoto N, Fuchimoto Y, and T. Kishimoto (Okayama Rosai Hospital); H. Kawai and K. Watanabe (Okayama Saiseikai General Hospital); K. Tokumo (Onomichi General Hospital); T. Murakami (Onomichi Municipal Hospital); T. Isobe and Y. Tsubata (Shimane University School of Medicine); M. Inoue (Shimonoseki City Hospital); H. Ichikawa (Takamatsu Hospital); Y. Nishioka, M. Hanibuchi, and H. Goto (Tokushima University Hospital); T. Sumikawa (Tottori Prefectural Central Hospital); M. Kodani, H. Suyama, H. Makino, Y. Ueda, N. Kinoshita, and E. Shimizu (Tottori University Hospital); H. Obata and H. Ikegami (Yamaguchi-ken Saiseikai Shimonoseki General Hospital); and Y. Kunihiro, T. Kobayashi, K. Ueda, M. Hayashi, M. Kamiya, and J. Murakami (Yamaguchi University Hospital).

LC-SCRUM group: S. Matsumoto and K. Goto.

Center for Innovative Clinical Medicine, Okayama University Hospital: K. Miyake, K. Ueda, H. Okuda, N. Kondoh, M. Fukata, S. Kuroda, S. Sugihara, M. Nakabayashi, N. Hiramatsu, S. Hinotsu, K. Zama, W. Ishii, Y. Ohe, C. Harada, M. Yoshida, K. Kamikawa, J. Sakurai, and K. Shikata.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2017.10.032.

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