Received: 2 June 2017 | Revised: 16 October 2017 | Accepted: 31 October 2017

DOI: 10.1111/cas.13436

ORIGINAL ARTICLE

WILEY Cancer Science

Potential utility of a longitudinal relative dose intensity of molecularly targeted agents in phase 1 dose-finding trials

Akihiro Hirakawa[1,2] | Kan Yonemori[2,3,4] | Fumie Kinoshita[5] | Yumiko Kobayashi[5] | Hitomi S. Okuma[2] | Asuka Kawachi[2] | Kenji Tamura[2] | Yasuhiro Fujiwara[2] | Larry Rubinstein[6] | Pamela Jo Harris[4] | Naoko Takebe[4]

[1]Department of Biostatistics and Bioinformatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[2]Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

[3]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

[4]Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institute of Health, Rockville, MD, USA

[5]Statistical Analysis Section, Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan

[6]Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institute of Health, Rockville, MD, USA

Correspondence
Akihiro Hirakawa, Department of Biostatistics and Bioinformatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.
Email: hirakawa@m.u-tokyo.ac.jp

Funding information
Japan Society for Promotion of Science KAKENHI (grant number 15K15948, and 17K00045); the Project Promoting Clinical Trials for Development of New Drugs and Medical Devices from the Japan Agency for Medical Research and Development (grant number 17lk0201044h0002).

Phase 1 trials of molecularly targeted agents (MTA) often do not use toxicity data beyond the first cycle of treatment to determine a recommended phase 2 dose (RP2D). We investigated the potential utility of longitudinal relative dose intensity (RDI) that may be a better new way of determining a more accurate RP2D as a lower dose that is presumably more tolerable over the long term without compromising efficacy. All consecutive patients who were initially treated using a single MTA at the conventional RP2D or at one level lower dose (OLLD) of that RP2D in 9 phase 1 trials sponsored by the National Cancer Institute were included. The associations between longitudinal RDI, time to first progression, and response rate were analyzed. The RDI of the conventional RP2D group were maintained a rate of ≥70% throughout 10 cycles, and were higher than those of the OLLD group, although in both groups the RDI gradually decreased with additional treatment cycles. The RP2D group was similar to the OLLD group with respect to time to first progression and response rate. In both groups, however, the decreasing RDI over time was significantly associated with shorter time to first disease progression; therefore, the longitudinal RDI, which takes into account lower grade toxicity occurrences, may be useful in determining a more desirable dose to use in phase 2 and 3 studies.

KEYWORDS
maximum tolerated dose, molecularly targeted agent, phase 1 trial, recommended phase 2 dose, relative dose intensity

1 | INTRODUCTION

The objective of phase 1 oncology trials is to determine the optimal dose of an agent or combination of agents that can be used as the recommended phase 2 dose (RP2D).[1] The conventionally-defined RP2D of a cytotoxic agent corresponds to the maximum tolerated dose (MTD), which is the highest clinically-safe dose that is determined from dose limiting toxicity (DLT) data obtained during the first and, occasionally, the second cycle of treatment. Toxicity data from later cycles is not used to determine the RP2D; furthermore, treatment changes (eg, dose reduction or treatment interruption) are recorded but not used to determine the RP2D.[2,3]

While such a conventional approach has been successful for evaluating cytotoxic agents, it may not be optimal to determine the RP2D of molecularly targeted agents (MTA).[4] In this regard, Le Tourneau et al.[5] recommend that treatment delay and/or reduction of relative dose intensity (RDI) be included in the definition of DLT. Other appropriate definitions of DLT discussed[6-9] include the choice of starting dose of MTA.[10] Moreover, there are patients who develop chronic low-grade toxicities from MTA during the evaluation period of phase 1 trials. Such events eventually warrant dose reduction or treatment interruption owing to intolerance. The conventional method for determining RP2D relies on the traditional definition of the MTD during cycle 1, wherein low-grade toxicities are not considered and excluded from MTD determination. These toxicities eventually become intolerable and are major factors leading to dose reduction or interruption following the cycle 1 evaluation period, resulting in insufficient drug exposure. The determination of a methodology to predict an appropriate MTA RP2D, instead of basing it on a simple MTD determination, has been advocated.

A recent workshop examined FDA-approved agents for oncology indications requiring dose reductions and interruptions in initial registration trials for small molecule kinase inhibitors.[11] Of 31 approved inhibitors, at least 8 necessitated post-marketing requirements or commitments. There is a significant gap in the development of these agents because of a failure to predict an appropriate administration dose, potentially leading to late-onset and/or cumulative toxicity.[12] Consequently, there is a need to assess the frequency of cases requiring MTA dose reduction after cycle 1, and to evaluate the duration and degree of dose lowering (ie, RDI).

Apart from MTD, a study on toxicity information in phase 1 MTA trials found that moderate and severe toxicities occur regularly after cycle 1, and attention on RP2D determination may be warranted.[3] It has been suggested that RP2D assessment should incorporate all available information from any cycle, including lower grade toxicities leading to decreased RDI.[3]

Relative dose intensity is defined as the ratio of the effectively delivered dose to the theoretically administered cumulative dose. In early disease, it is considered that the clinical outcome for patients receiving a higher RDI is better than for those receiving a lower RDI.[13-15] The impact of RDI on survival in advanced/metastatic cancer has been inadequately studied, although it has been individually evaluated in several other cancers and treatment settings.[16-19] Recently, a review reported that in a few studies, there was an association between RDI and survival outcome in some patients with metastatic cancer, an issue which has also been highlighted in other studies.[20-22]

In this study, a comprehensive analysis of RDI was carried out to address 2 issues for determination of a more accurate RP2D: (i) the degree to which RDI is reduced in later cycles during RP2D and one level lower dose (OLLD) of the RP2D uses in phase 1 trials, and whether initial dose (ie, the RP2D or OLLD) matters; and (ii) whether a reduced RDI is associated with poor clinical outcomes, such as shorter time to disease progression or lower response rates. To this end, we defined the RDI for each patient as the ratio of the RP2D (or OLLD) delivered to the theoretically administered cumulative RP2D at every cycle during the trial in the RP2D (or OLLD) group. The associations between the RDI over the long term, time to progression, and response rate between the 2 groups were assessed. These issues cannot be assessed with data from phase 2 or 3 trials because they use a single RP2D of the investigational drug determined from phase 1 trials. Therefore, we used integrated data from the 9 phase 1 trials, sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI). We also investigated the grade of observed toxicity and changes in treatment due to the occurrences of toxicity, possibly decreasing RDI over the long term.

2 | MATERIALS AND METHODS

2.1 | Evaluation of phase 1 trials

Data from patients enrolled in the CTEP-sponsored phase 1 clinical oncology trials in which the test article was a single MTA were assessed between March 2000 and December 2012. The data were extracted prospectively from the Clinical Trials Monitoring System database managed by Theradex Systems (Princeton, NJ, USA). We included only phase 1 trials of a single MTA and excluded combinations of multiple agents (Figure 1). Among the 102 phase 1 trials, 83 were excluded for the following reasons: (i) 54 involved cytotoxic agents and/or only enrolled patients with hematologic malignancies; (ii) 18 involved renal/kidney dysfunction patients; and (iii) the objective of 11 was not dose-finding. Ten trials that did not reach the MTD were also excluded. For the remaining 9 trials, we collected data on target tumor type, class of agent, administration route, dose-finding design used and number of dose levels.

2.2 | Data collection

For each trial, we extracted data for patients who were initially treated at the conventional RP2D (termed the RP2D group) or OLLD than the conventional RP2D (termed the OLLD group). Data collected for each patient included age, sex, race, performance status (PS), trial start and end dates, grading of any toxicities including the protocol-

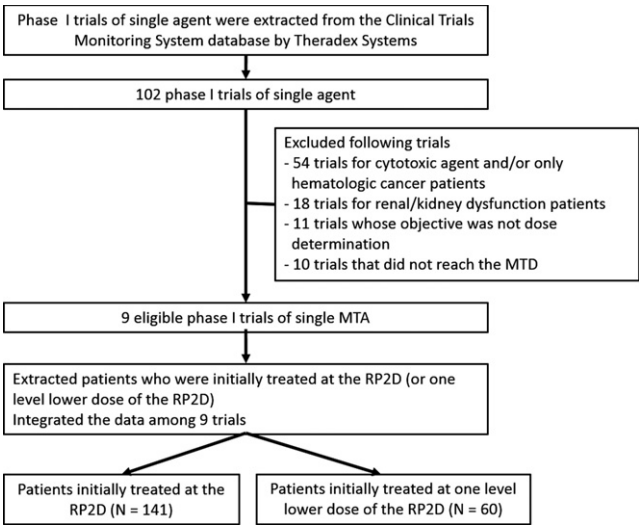

FIGURE 1 Flowchart of the study. MTA, molecularly targeted agent; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

defined DLT occurring in each cycle and date of occurrence, and treatment provided (eg, none, dose reduced, regimen interrupted, therapy discontinued, and interrupted and then reduced), tumor response and RDI in each cycle, and reason for dropout during the trials. Data on grade 1-5 toxicities for all cycles of every trial were collected according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 2.0, 3.0 or 4.0). Response and progression of each solid tumor were evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. Evaluation of the response for non-Hodgkin's lymphoma followed the International Working Group Standardized Response Criteria. These evaluations were conducted every 8-12 weeks in almost all trials. A treatment cycle, defined in the corresponding protocol of the trial, was used as the time unit irrespective of the duration in terms of number of days.

2.3 | Statistical analysis

Prevalence was calculated as the ratio of the number of patients to the total number of patients. Time to the event of interest was defined as the time between the start date of treatment and the occurrence of that event. Survival curves were calculated using the Kaplan-Meier method. Patients who died during the trials were censored at the time of death. The RDI in each cycle for the 2 groups was estimated using the random effect model, because the patient numbers in the trial gradually decreased with increasing cycles. To evaluate the association between the RDI over the long term and the time to disease progression and tumor response, we performed Cox regression analysis, with the RDI included as a time-varying covariate, and logistic regression analysis. The 3 models commonly included the following variables: dose group (RP2D vs OLLD), age (<65 vs ≥65 years), sex (female vs male), PS (0 vs 1 or 2) and administration route (intravenous vs oral). Kaplan-Meier curves with information on the RDI were also graphed.[23] All statistical tests were 2-sided. $P < .05$ was considered statistically significant. All the analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Trial and patient characteristics

The characteristics of 9 phase 1 dose-finding trials are shown in Table 1. Five trials included only patients with any solid tumors (one trial with only patients with gynecologic cancer), and 4 trials included solid tumors or lymphoma. Most of the agents evaluated in our study were small molecule tyrosine kinase inhibitors (TKI) (78%). The routes of MTA administration were oral for 6 trials (67%) and intravenous for 3 (33%). The 3 + 3 design was used in 7 trials (78%). The median number of dose levels in l the trials was 6 (range 5-10).

The patient characteristics are listed in Table 2. The number of patients receiving the conventional RP2D (n = 141) was more than double that receiving OLLD (n = 60). This result is because in phase 1 trials, a larger number of patients are generally enrolled in the RP2D cohort for safety confirmation than in the OLLD group. The median number of patients per trial in the conventional RP2D and OLLD groups was 14 and 5, respectively. The distributions of age, sex, race and PS were almost the same for both groups.

3.2 | Prevalence of toxicity and treatment management change

We evaluated the prevalence of any grade toxicity and treatment management in the RP2D and OLLD groups through 10 cycles

TABLE 1 Trial characteristics of the 9 phase 1 trials involving a single molecularly targeted agents

Variables		n (%)
Trial		
Tumor type	Solid	5 (56)
	Solid or lymphoma	4 (44)
Class of agent	Small molecule tyrosine kinase inhibitors	7 (78)
	Antibody	1 (11)
	Alkylphospholipid	1 (11)
Administration route	Oral	6 (67)
	Intravenous	3 (33)
Dose-finding design used	Rule-based design such as 3 + 3 design	7 (78)
	Accelerated titration design	2 (22)
Number of dose level	Median	6
	Range	5-10
	5	2 (22)
	6	4 (44)
	7	1 (11)
	10	2 (22)

TABLE 2 Patient characteristics in trials receiving the RP2D or one level lower of the RP2D

Variables		Patients initially treated at RP2D (RP2D group)	Patients initially at one level lower dose of RP2D (OLLD group)
Total number of patients		141	60
Number of patients per trial	Median	14	5
	Range	6-41	1-17
Age, years	Median	55	59
	Range	20-85	22-83
Sex, n (%)	Male	57 (40)	26 (43)
	Female	84 (60)	34 (57)
Race, n (%)	White	118 (84)	57 (95)
	Black	14 (10)	2 (3)
	Asian	7 (5)	1 (2)
	Others	2 (1)	0 (0)
PS, n (%)	0	36 (26)	14 (23)
	1	101 (72)	44 (73)
	2	3 (2)	2 (3)

OLLD, one level lower dose of RP2D; PS, performance status; RP2D, recommended phase 2 dose.

(Table 3). Careful interpretation of the comparative result of toxicity prevalence between the 2 groups through 10 cycles was required because the number of patients in the trials gradually decreased with increasing cycles. The reasons for patient drop out of the studies are summarized in Table S1.

As listed in Table 3 and Table S2, in the RP2D group, grade 3 and 4 toxicities (44.7% and 3.5%) occurred in cycle 1. In the OLLD groups, grade 3 and 4 toxicities (48.3% and 3.3%) occurred in cycle 1. All grades of toxicity in the 2 study groups occurred at constant rates in 10 cycles.

The prevalence of dose reductions in the conventional RP2D group was slightly higher than in the OLLD group until cycle 5. The prevalence of regimen interruptions was commonly higher than that of any other treatment management changes in both groups. The prevalence of regimen interrupted, therapy discontinued, and interrupted and then reduced were similar in both groups.

We also noted the times to initial toxicity of any grade, any grade to the worst grade, and to grades 3 to 4 (Figure 2) through 20 cycles; these were similar in the conventional RP2D and OLLD groups. The following general trends were observed in both groups: during cycle 1, approximately 100% of the patients developed some grade of toxicity (Figure 2A) and 70% developed their worst-grade toxicity (Figure 2B); approximately 40% developed grades 3 and 4 toxicities during cycle 1 with their subsequent occurrence at a constant rate (Figure 2C); for time to first treatment management change, these occurred at a constant rate from cycles 1 to 8 and were then lower after that (Figure 2D-G).

3.3 | Relative dose intensity in the 10 longitudinal study cycles

The RDI values of subjects who received treatment through 10 longitudinal study cycles were estimated using the random effect model (see Table 3). The RDI of the RP2D group were maintained at the rate of ≥70% throughout 10 cycles, and were higher than those of the OLLD group that ranged from 43.0% to 71.1%, although the RDI decreased in both groups with increasing treatment cycle. The proportions of patients with RDI ≥75% in the RP2D group were also higher than those in the OLLD group in all cycles. The average RDI for patients who dropped out of the study in the 2 groups were <70% in almost all cycles of treatment (Table S1).

3.4 | Association between longitudinal relative dose intensity and clinical outcome

For each group, patients were categorized into 3 subgroups based on the RDI at each cycle (eg, low group showing RDI <50%, moderate group showing RDI 50%-75%, and high group showing RDI ≥75%), with Kaplan-Meier curves of the time to first disease progression (PD) drawn for each. In the both groups, the significant difference between the low and high RDI subgroups was determined using the log-rank test ($P < .05$, Figure 3A,B).

Furthermore, the multivariate Cox regression analysis, with the RDI included as a time-varying covariate, showed that the time to first PD between the RP2D and OLLD groups was similar (hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.74-1.56, $P = .705$) (see Table S3 and Figure 4), but suggested that a 10% decrease in RDI significantly shortened the time to first PD (HR, 1.12; 95% CI, 1.06-1.20, $P < .001$).

In addition, the rates of complete/partial responses (CR/PR), stable disease (SD) and PD for the RP2D group were 10.9% (13/119), 31.9% (38/119) and 57.1% (68/119), respectively, and those for the OLLD group were 1.9% (1/53), 32.1% (17/53) and 66.0% (35/53), respectively. No associations between the dose group (or average RDI) and response rate were found in the multivariate logistic regression analysis (Table S4), but the difference in the response rate between the 2 groups (ie, 10.9% of RP2D group vs 1.9% of OLLD group) was shown to be marginally significant by Fisher's exact test ($P = .067$). The RDI of the 14 patients with CR/PR were maintained a rate of ≥75% throughout (see Table S5). The RDI mean values in the RP2D group in the first 10 cycles for patients presenting CR/PR, SD and PD as the best response were 90% (n = 13), 88% (n = 38) and 81% (n = 68) respectively, and those in the OLLD group were 80% (n = 1), 88% (n = 17) and 86% (n = 35).

4 | DISCUSSION

The conventional RP2D is based solely on toxicity data from cycle 1 for MTA, despite this erroneous determination being identified as a significant cause for failure in the development of new agents in

TABLE 3 Prevalence of toxicities, treatment management changes and longitudinal RDI throughout 10 cycles

		Cycle									
	Group	1	2	3	4	5	6	7	8	9	10
Number of patients, n	RP2D	141	101	48	41	27	26	21	18	12	9
	OLLD	60	42	15	11	8	7	6	5	3	3
Toxicity											
Prevalence of grade 1 toxicity, %	RP2D	99.3	99.0	100.0	97.6	96.3	100.0	95.2	100.0	91.7	100.0
	OLLD	100.0	97.6	93.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Prevalence of grade 2 toxicity, %	RP2D	80.1	80.2	54.2	65.9	48.1	42.3	47.6	44.4	58.3	66.7
	OLLD	75.0	73.8	80.0	90.9	87.5	71.4	83.3	60.0	100.0	100.0
Prevalence of grade 3 toxicity, %	RP2D	44.7	34.7	22.9	24.4	14.8	11.5	19.0	22.2	16.7	0.0
	OLLD	48.3	45.2	40.0	27.3	50.0	42.9	16.7	40.0	33.3	66.7
Prevalence of grade 4 toxicity, %	RP2D	3.5	3.0	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0
	OLLD	3.3	9.5	13.3	9.1	12.5	14.3	16.7	20.0	33.3	33.3
Prevalence of grade 5 toxicity, %	RP2D	2.1	1.0	0.0	0.0	0.0	0.0	0.0	0.0	8.3	0.0
	OLLD	1.7	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Prevalence of DLT, %	RP2D	6.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8.3	0.0
	OLLD	5.0	2.4	0.0	0.0	0.0	0.0	16.7	20.0	33.3	33.3
Treatment management changes											
Prevalence of dose reduced, %	RP2D	9.2	3.0	4.2	2.4	3.7	0.0	0.0	0.0	0.0	0.0
	OLLD	1.7	2.4	0.0	0.0	12.5	0.0	16.7	20.0	33.3	33.3
Prevalence of regimen interrupted, %	RP2D	17.0	14.9	12.5	7.3	3.7	0.0	4.8	5.6	8.3	0.0
	OLLD	15.0	19.0	26.7	27.3	25.0	28.6	16.7	20.0	33.3	33.3
Prevalence of therapy discontinued, %	RP2D	5.7	5.0	0.0	4.9	0.0	0.0	9.5	0.0	16.7	0.0
	OLLD	10.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Prevalence of interrupted and then reduced, %	RP2D	5.7	0.0	0.0	2.4	3.7	0.0	0.0	0.0	0.0	0.0
	OLLD	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RDI											
RDI, %	RP2D	86.4	78.0	80.0	75.3	78.7	78.0	72.1	71.8	72.3	77.1
	OLLD	71.1	58.0	65.1	63.6	61.4	63.8	43.0	56.3	53.4	54.1
Proportion of patients with RDI ≥75%, %	RP2D	76.6	70.3	81.3	75.6	85.2	84.6	76.2	77.8	58.3	88.9
	OLLD	45.0	35.7	33.3	45.5	37.5	28.6	0.0	20.0	0.0	0.0
Proportion of patients with 50% ≤RDI <75%, %	RP2D	14.2	13.9	10.4	12.2	7.4	11.5	14.3	16.7	41.7	11.1
	OLLD	38.3	38.1	53.3	36.4	37.5	57.1	83.3	80.0	100.0	100.0
Proportion of patients with RDI <50%, %	RP2D	9.2	15.8	8.3	12.2	7.4	3.8	9.5	5.6	0.0	0.0
	OLLD	16.7	26.2	13.3	18.2	25.0	14.3	16.7	0.0	0.0	0.0

DLT, dose limiting toxicity; OLLD, one level lower dose of RP2D; RDI, relative dose intensity; RP2D, recommended phase 2 dose.
Protocol-specified grade 3 or grade 4 hematologic and/or non-hematologic toxicities were defined as DLT in all the 9 trials evaluated, while grade 2 toxicity was also included in 2 trials. All the 9 trials prescribed rules for treatment changes within the protocol. In some trials, dose reduction rules for grades 2-4 were provided separately.

oncology.[24,25] The apparent relationship between the clinical benefit and MTA dose level was not determined in some studies owing to probably faulty determination of RP2D[26,27] A study reported that phase 1 MTA trials have probably underestimated toxicity in dose recommendations.[28] However, another study suggested that there are clinical benefits of improved response and overall survival with increasing doses in phase 1 MTA trials.[29] To address this controversial issue and to improve the selection rates for true RP2D, efficient utilization of RDI over the long term should be considered.

Our results suggested that in both RP2D and OLLD groups, grade 3 and 4 toxicities occurred through all 10 study cycles at a constant rate. Although the incidences of grade 3 and 4 toxicities were higher in the OLLD group than in the RP2D group, the toxicities in both groups were not significantly different for most of the cycles (results not shown). Therefore, it appears that the potential incidence of grade 3 and 4 toxicities is similar between the 2 groups. In both RP2D and OLLD, the treatment changes groups followed a similar pattern and commonly decreased the longitudinal RDI. However, the

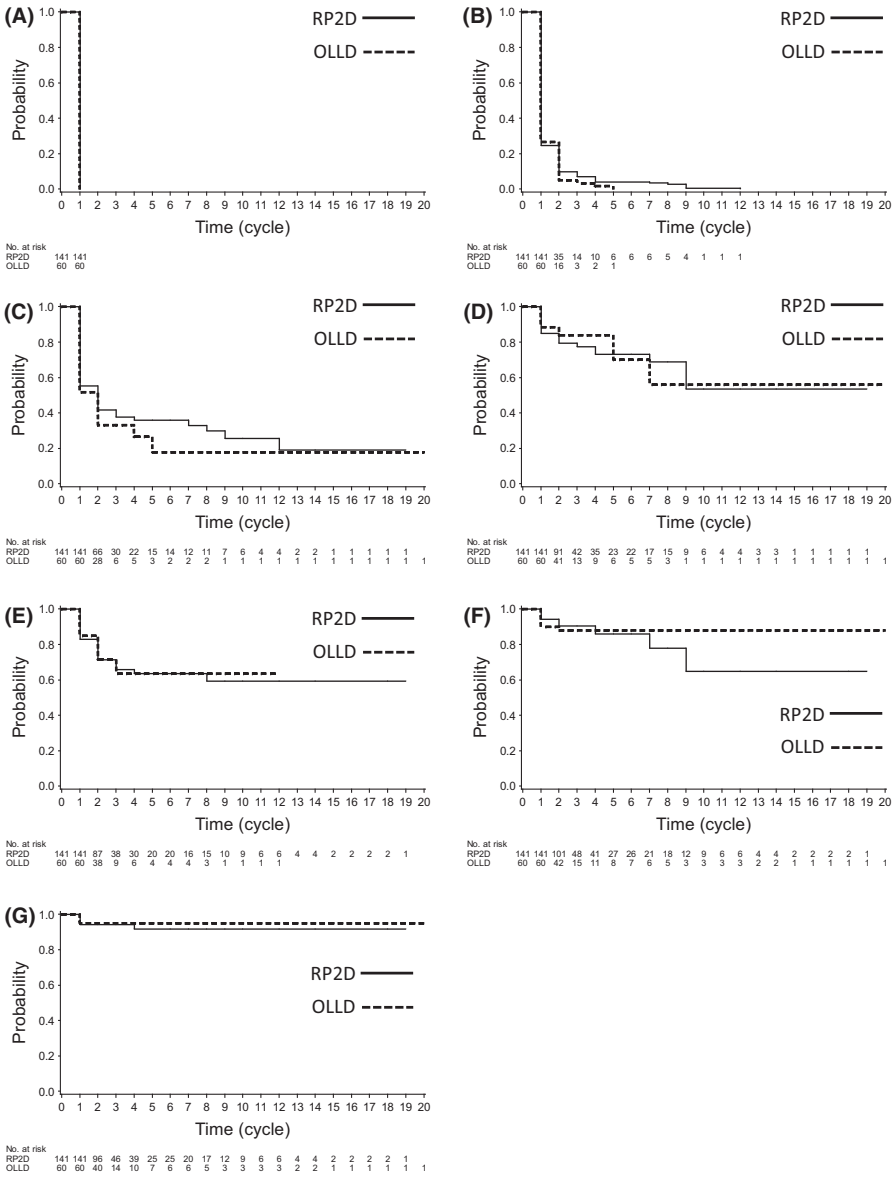

FIGURE 2 Time to toxicity and treatment management changes. The solid and dotted lines represent RP2D and OLLD groups, respectively. A, Time to first toxicity of any grade. B, Time to the worst-grade toxicity. C, Time to grade 3 or 4 toxicity. D, Time to the first dose reduction or therapy discontinuation. E, Time to first regimen interruption. F, Time to first therapy discontinuation. G, Time to first regimen interruption and subsequent dose reduction. OLLD, one level lower dose of RP2D; RP2D, recommended phase 2 dose

longitudinal RDI in the RP2D group was maintained at a higher rate compared to those in the OLLD group for all the cycles. Furthermore, the RP2D group was similar to the OLLD group with respect to the time to first PD and response rate. Therefore, the standard RP2D, determined based on the usual dose-finding method using only toxicity data during cycle 1 of treatment, would not only be the MTD but also the continuously administered dose. Notably, the definitive comparison between the efficacy of the RP2D and OLLD dose levels needs to be done in a phase 3 (or, at the least, a phase 2) trial.

In contrast, the 10% decrease in RDI over time was significantly associated with the shortened time to first progression. In addition, the longitudinal RDI of the dropout patients were lower than those in the patients continuing treatment by approximately 10%-20% in the early cycles of treatment. These results indicated that the standard RP2D may not be optimal as the dose for longitudinal use to achieve better clinical outcome; therefore, we may need to consider longitudinal RDI in determining the RP2D in phase 1 trials. In this context, it may be reasonable to carefully evaluate the OLLD of the RP2D as an alternative dose for further testing in addition to the standard RP2D. More conservatively, the benefit–risk balances between the standard RP2D and its OLLD should be compared for subsequent phase 2 (or 3) trials.

In practice, however, the minimum RDI to be reached must be questioned. The consensus among experts in drug development is that a threshold of >75% of the intended RDI is acceptable;[3] however, this threshold is only a guideline. The results also showed that no <20% of the patients had an RDI <75% throughout all 10 cycles in the RP2D group. Practically, the target RDI may be varied depending on several characteristics, such as agent type, target population and administration route.

In conclusion, our finding of this study was that in both groups the RDI over time was significantly associated with shorter time to first disease progression; therefore, the longitudinal RDI, which takes into account lower grade toxicity occurrences, may be useful in

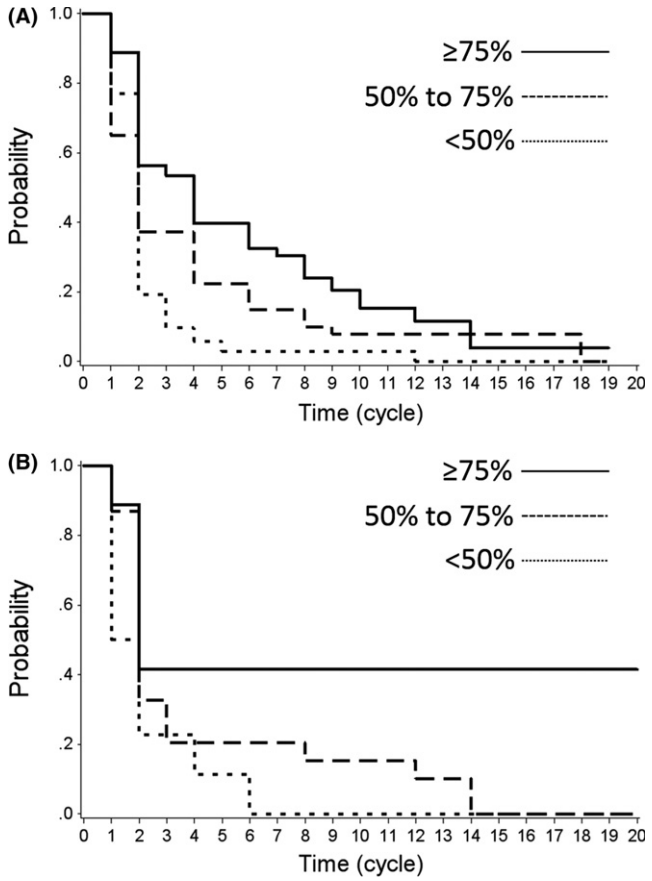

FIGURE 3 Kaplan-Meier curves for the time to first progression of the 3 groups based on the time-varying covariate of longitudinal RDI: (A) RP2D group and (B) OLLD group. Specifically, the dotted line represents <50% of RDI, the dashed line represents 50%-75% of RDI, and the solid line represents ≥75% of RDI. Notably, unlike standard Kaplan-Meier curves, the extended curves do not correspond to fixed cohorts of patients; therefore, patients can contribute to different curves at different cycles. OLLD, one level lower dose of RP2D; RDI, relative dose intensity; RP2D, recommended phase 2 dose

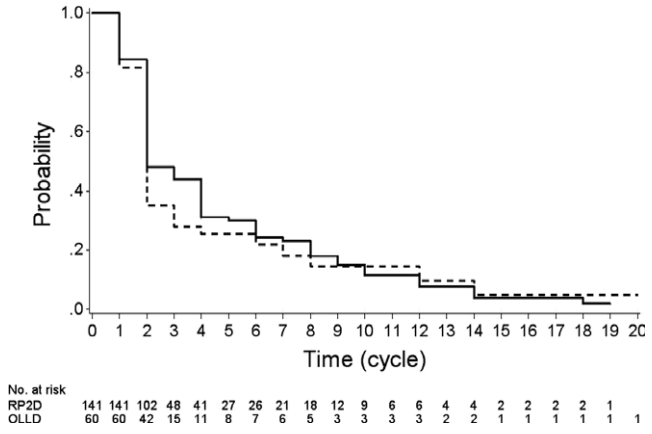

FIGURE 4 Kaplan-Meier curves for the time to first progression in RP2D and OLLD groups. The solid and dotted lines represent RP2D and OLLD groups, respectively. OLLD, one level lower dose of RP2D; RP2D, recommended phase 2 dose

determining a more desirable dose to use in phase 2 and 3 studies. These findings indicated the need for further investigations to address whether a "true" RP2D can be predicted through statistical modeling, so that a patient could tolerate the same dose for a reasonable duration of time and not require significant dose reduction or pauses. If a "true" RP2D can be modeled, then a randomized clinical trial will be required to compare whether such a non-standard RP2D and a standard estimated RP2D will result in different clinical outcomes, including progression-free or overall survival.

We investigated the toxicities of small molecule TKI as MTA, and did not include sufficient antibody agents or immunotherapies; therefore, our findings are not generalizable. Second, the number of patients in the trials gradually decreased with increasing cycles; hence, the impact of RDI observed should be carefully interpreted. Finally, our results are based on only 9 phase 1 trials, but the study involved the careful examination of the protocols and data of the 102 phase 1 trials in order to properly compare the longitudinal toxicity and efficacy outcomes between the RP2D and OLLD groups.

Phase 1 patients are not necessarily representative of the larger patient population receiving MTA. This question of optimal dose, with respect to efficacy and toxicity, may require testing in phase 2 or phase 3.

ACKNOWLEDGEMENTS

This work was partially supported by the Japan Society for Promotion of Science KAKENHI (grant number 15K15948, and 17K00045) and the Project Promoting Clinical Trials for Development of New Drugs and Medical Devices from the Japan Agency for Medical Research and Development (grant number 17lk0201044h0002).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Akihiro Hirakawa http://orcid.org/0000-0003-2580-7460
Kenji Tamura http://orcid.org/0000-0002-3514-9927

REFERENCES

1. Oncology ASoC. Critical role of phase 1 clinical trials in cancer treatment. *J Clin Oncol*. 1997;15:853-859.
2. Postel-Vinay S, Gomez-Roca C, Molife LR, et al. Phase 1 trials of molecularly targeted agents: should we pay more attention to late toxicities? *J Clin Oncol*. 2011;29:1728-1735.
3. Postel-Vinay S, Collette L, Paoletti X, et al. Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents–dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted therapies, an European Organisation for Research and Treatment of Cancer-led study. *Eur J Cancer*. 2014;50:2040-2049.

4. Le Tourneau C, Diéras V, Tresca P, et al. Current challenges for the early clinical development of anticancer drugs in the era of molecularly targeted agents. *Target Oncol*. 2010;5:65-72.
5. Le Tourneau C, Razak AR, Gan HK, et al. Heterogeneity in the definition of dose-limiting toxicity in phase 1 cancer clinical trials of molecularly targeted agents: a review of the literature. *Eur J Cancer*. 2011;47:1468-1475.
6. Penel N, Adenis A, Clisant S, et al. Nature and subjectivity of dose-limiting toxicities in contemporary phase 1 trials: comparison of cytotoxic versus non-cytotoxic drugs. *Invest New Drugs*. 2011;29:1414-1419.
7. Iasonos A, Gounder M, Spriggs DR, et al. The impact of non-drug-related toxicities on the estimation of the maximum tolerated dose in phase 1 trials. *Clin Cancer Res*. 2012;18:5179-5187.
8. Paoletti X, Le Tourneau C, Verweij J, et al. Defining dose-limiting toxicity for phase 1 trials of molecularly targeted agents: results of a DLT-TARGETT international survey. *Eur J Cancer*. 2014;50:2050-2056.
9. Drilon A, Eaton AA, Schindler K, et al. Beyond the dose-limiting toxicity period: dermatologic adverse events of patients on phase 1 trials of the Cancer Therapeutics Evaluation Program. *Cancer*. 2016;122:1228-1237.
10. Le Tourneau C, Stathis A, Vidal L, et al. Choice of starting dose for molecularly targeted agents evaluated in first-in-human phase 1 cancer clinical trials. *J Clin Oncol*. 2010;28:1401-1407.
11. Jänne PA, Kim G, Shaw AT, et al. Dose finding of small-molecule oncology drugs: optimization throughout the development life cycle. *Clin Cancer Res*. 2016;22:2613-2617.
12. Nie L, Rubin EH, Mehrotra N, et al. Rendering the 3 + 3 design to rest: more efficient approaches to oncology dose-finding trials in the era of targeted therapy. *Clin Cancer Res*. 2016;22:2623-2629.
13. Nemet D, Piura B, Cohen Y, et al. Dose intensity of cisplatin-based chemotherapy in epithelial ovarian carcinoma. An important factor affecting survival. *Eur J Gynaecol Oncol*. 1995;16:107-114.
14. Frei E, Elias A, Wheeler C, et al. The relationship between high-dose treatment and combination chemotherapy: the concept of summation dose intensity. *Clin Cancer Res*. 1998;4:2027-2037.
15. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol*. 2003;21:4524-4531.
16. French Epirubicin Study Group. Epirubicin-based chemotherapy in metastatic breast cancer patients: role of dose-intensity and duration of treatment. *J Clin Oncol*. 2000;18:3115-3124.
17. Terada Y, Nakamae H, Aimoto R, et al. Impact of relative dose intensity (RDI) in CHOP combined with rituximab (R-CHOP) on survival in diffuse large B-cell lymphoma. *J Exp Clin Cancer Res*. 2009;28:116.
18. Bouvet E, Borel C, Obéric L, et al. Impact of dose intensity on outcome of fludarabine, cyclophosphamide, and rituximab regimen given in the first-line therapy for chronic lymphocytic leukemia. *Haematologica*. 2013;98:65-70.
19. Porta C, Levy A, Hawkins R, et al. Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. *Cancer Med*. 2014;3:1517-1526.
20. Havrilesky LJ, Reiner M, Morrow PK, et al. A review of relative dose intensity and survival in patients with metastatic solid tumors. *Crit Rev Oncol Hematol*. 2015;93:203-210.
21. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol*. 1984;2:1281-1288.
22. Fizazi K, Ducreux M, Ruffié P, et al. Phase 1, dose-finding, and pharmacokinetic study of raltitrexed combined with oxaliplatin in patients with advanced cancer. *J Clin Oncol*. 2000;18:2293-2300.
23. Xu S, Shetterly S, Powers D, et al. Extension of Kaplan–Meier methods in observational studies with time-varying treatment. *Value Health*. 2012;15:167-174.
24. Booth CM, Calvert AH, Giaccone G, et al. Endpoints and other considerations in phase 1 studies of targeted anticancer therapy: recommendations from the task force on Methodology for the Development of Innovative Cancer Therapies (MDICT). *Eur J Cancer*. 2008;44:19-24.
25. Ratain MJ, Stadler WM. Clinical trial designs for cytostatic agents. *J Clin Oncol*. 2001;19:3154-3155.
26. Postel-Vinay S, Arkenau HT, Olmos D, et al. Clinical benefit in phase 1 trials of novel molecularly targeted agents: does dose matter? *Br J Cancer*. 2009;5100:1373-1378.
27. Moreno García V, Olmos D, Gomez-Roca C, et al. Dose–response relationship in phase 1 clinical trials: a European Drug Development Network (EDDN) Collaboration Study. *Clin Cancer Res*. 2014;20:5663-5671.
28. Roda D, Jimenez B, Banerji U. Are doses and schedules of small-molecule Targeted anticancer drugs recommended by phase 1 studies realistic? *Clin Cancer Res*. 2016;22:2127-2132.
29. Gupta S, Hunsberger S, Boerner SA, et al. Meta-analysis of the relationship between dose and benefit in phase 1 targeted agent trials. *J Natl Cancer Inst*. 2013;104:1860-1866.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Hirakawa A, Yonemori K, Kinoshita F, et al. Potential utility of a longitudinal relative dose intensity of molecularly targeted agents in phase 1 dose-finding trials. *Cancer Sci*. 2018;109:207–214. https://doi.org/10.1111/cas.13436