Original

Prognostic significance of 8 weeks’ relative dose intensity of lenvatinib in treatment of radioiodine-refractory differentiated thyroid cancer patients

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Abstract. Lenvatinib is a standard therapy for radioiodine-refractory differentiated thyroid cancer (RR-DTC). However, because of the high incidence of adverse events resulting from this treatment, it is not easy to maintain the dose intensity of lenvatinib, especially in Japanese patients. Although the prognostic impact of lenvatinib dose interruption has been reported, the target dose intensity of lenvatinib to optimize survival benefits remains unknown. We therefore propose a target dose intensity of lenvatinib during the first 8 weeks of treatment. We retrospectively analyzed 42 RR-DTC patients who were treated with lenvatinib for more than 8 weeks. We performed receiver operating characteristic curve analysis to determine the cut-off value of 8 weeks’ relative dose intensity (8w-RDI) to predict treatment response, and identified that the optimal cut-off value of 8w-RDI was 60% (sensitivity: 81.8%; specificity: 80.6%). Median progression-free survival (PFS) (not reached [NR] vs. 11.0 months; hazard ratio [HR] 0.29; 95% confidence interval [CI] 0.11–0.72; \( p < 0.01 \)) and overall survival (NR vs. 27.6 months; HR 0.44; 95% CI 0.11–0.91; \( p = 0.03 \)) were longer in the higher 8w-RDI ( \( \geq 60\% \) ) patients than in the lower 8w-RDI ( <60% ) patients. Multivariate analysis revealed that 8w-RDI at \( \geq 60\% \) was an independent prognostic factor for PFS (HR 0.29; 95% CI 0.09–0.96; \( p = 0.04 \)). Targeting for \( \geq 60\% \) of the relative dose intensity during the first 8 weeks of lenvatinib treatment can be sufficient to achieve significant tumor shrinkage and prolong PFS in RR-DTC patients.

Key words: Differentiated thyroid cancer, Lenvatinib, Relative dose intensity

THE INCIDENCE OF THYROID CANCER is increasing worldwide. According to the GLOBOCAN, there were 567,000 new cases of thyroid cancer and an estimated 41,000 related deaths in 2018 [1]. Although most differentiated thyroid cancers are observed as slow-growing neoplasms, even in metastatic cases, some patients present with an aggressive course, typically resulting in death. The 10-year survival rate for stage IV patients is reported to be 37.0%, but once the patients become radioiodine-refractory, the mean life expectancy drops to 3–5 years [2, 3].

In the phase 3 SELECT (Study of E7080 “LEnvatinib” in differentiating Cancer of the Thyroid) trial, lenvatinib, an oral multi-kinase inhibitor against vascular endothelial growth factor receptors (VEGFRs) 1–3, fibroblast growth factor receptors (FGFRs) 1–4, the RET proto-oncogene, the stem cell factor receptor (KIT), and platelet-derived growth factor receptor alpha (PDGFRα), demonstrated prolonged progression-free survival (PFS) compared with placebo [18.3 versus 3.6 months, hazard ratio (HR) 0.21, \( p < 0.001 \)] for patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC) [4].

In a post hoc analysis of the SELECT trial, the median PFS of patients who required a longer dose interruption ( \( \geq 10\% \) of total treatment duration) was shorter than that of patients with a shorter dose interruption ( <10%). The median dose intensity of lenvatinib was lower in the longer dose-interruption group (14.6 mg/day) than in the shorter dose-interruption group (20.1 mg/day) [5]. These results indicate the importance of maintaining the dose intensity of lenvatinib for RR-DTC patients. However, the incidence of several treatment-related adverse events,
such as hypertension, proteinuria, and palmar-plantar erythrodysesthesia syndrome, was higher in the Japanese population than in the overall population; consequently, the Japanese patients underwent more dose reductions than the overall population (90.0% vs. 67.8%) [6]. Indeed, the mean dose of lenvatinib during the treatment was 12.06 mg/day in the post-marketing surveillance in Japan, which was lower than the dose reported in the SELECT trial (17.2 mg/day) [7].

Because most patients require dose reductions and interruptions of lenvatinib after adverse events, the longer the patients continue lenvatinib, the easier it is to decrease the mean or median dose intensity during the whole treatment period. Therefore, the dose intensity during the whole treatment period cannot always be a marker for successful treatment. In the SELECT trial, the median time to tumor response was 2 months [95% confidence interval (CI) 1.9–3.5 months] after lenvatinib induction, and the tumor shrinkage was greatest during the initial 8 weeks [4, 8]. In addition, the exposure to lenvatinib (area under the curve) correlated with greater tumor reduction during the first 8 weeks [8]. However, the dose intensity of lenvatinib that should be maintained during the first 8 weeks of treatment remains unclear. Here we investigated the sufficient target dose intensity of lenvatinib during the first 8 weeks, and evaluated the prognostic impact of 8 weeks’ relative dose intensity (8w-RDI) of lenvatinib for RR-DTC patients.

Materials and Methods

We retrospectively reviewed the medical records of recurrent or metastatic patients with RR-DTC who were treated with lenvatinib from January 2012 to July 2020 at the Department of Medical Oncology of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. The treatment consisted of once-daily oral dosing with 24 mg lenvatinib. Patients initially visited the outpatient every 2 weeks to assess treatment compliance and adverse effects, until adverse events were controlled for the first few months of therapy. After the adverse events were controlled, patients visited the outpatient every 2 to 8 weeks according to the treatment plan. The patients underwent routine computed tomography (CT) evaluation once every 2 to 4 months in most cases. Treatment interruptions and dose reductions were permitted by the treating physician according to the standard practice at our institute at the time of the trial. Treatment was continued until disease progression, the occurrence of unacceptable toxicity despite appropriate dose reduction and/or interruption, or the patient’s refusal of treatment. As we aimed to investigate long term survival impact of 8w-RDI, and as 8w-RDI cannot exactly calculated for patients who could not continue lenvatinib over 8 weeks, patients who discontinued lenvatinib within 8 weeks were excluded regardless of the reason for discontinuation.

Treatment response was evaluated by CT scans according to Response Evaluation Criteria in Solid Tumors (RECIST) (ver. 1.1) [9]. The overall response rate (ORR) was defined as the percentage of patients with a best overall response of either complete response (CR) or partial response (PR). The disease control rate (DCR) was the percentage of patients with a best overall response of CR, PR, or stable disease (SD). PFS was defined as the time from the first day of treatment to either the first objective evidence of disease progression or death from any cause. Overall survival (OS) was defined as the time from the first day of treatment to death by any cause. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. We also set cut-off period of RDI at 8 weeks as it is reported that the tumor response is greatest during the first 8 weeks in the SELECT trial. 8w-RDI of lenvatinib was calculated as the ratio of the actual dose intensity to the scheduled full dose intensity (24 mg/day for 56 days) during the first 8 weeks of lenvatinib treatment. Depth of response (DpR) was defined as the percentage (compared with baseline) of tumor shrinkage in the sum of the longitudinal diameters of target lesions at their smallest attained sizes.

EZR software (R ver. 4.0.2) (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for statistical analyses [10]. PFS and OS were estimated by the Kaplan–Meier method and were compared using the log-rank test. The survival results were expressed as the median value with a 95% CI. Wilcoxon signed-rank test was applied to analyze continuous data. Fisher’s exact test was applied to compare categorical variables. The Cox hazard regression model was used to analyze prognostic factors.

This study was approved by the institutional review board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (2020-1032), and was conducted in accordance with the Helsinki Declaration of 1964 and later versions.

Results

Patients’ characteristics

Between January 2012 and July 2020, 49 patients with RR-DTC were treated with lenvatinib. Among them, 42 patients who continued lenvatinib for more than 8 weeks were eligible for the analysis. Baseline patient characteristics are described in Table 1. The median age was 69 years (range, 22–83), and 16 (38.1%) patients were men.
The histological subtypes were papillary thyroid cancer (PTC) in 38 (90.5%) patients and follicular thyroid cancer (FTC) in four (9.5%). Metastatic sites were lung in 37 (88.1%) patients, lymph node in 22 (52.4%), bone in eight (19.1%), and liver in four (9.5%). All the patients had received surgery for the primary tumor. The mean cumulative dose of prior iodine-131 therapy was 155.7 mCi (standard deviation [SD] = 102.7). Seven (16.7%) patients had previously received sorafenib, and one (2.4%) patient had previously received vandetanib. The median thyroglobulin doubling time was 0.8 years (range, –0.37–21.88).

**Treatment delivery**

At the data collection cut-off of September 19, 2020, the median follow-up time for all enrolled patients was 16.4 months (range, 2.5–88.1). The starting dose of lenvatinib was 24 mg in 29 (69.1%) patients, 20 mg in 10 (23.8%), and 14 mg in three (7.1%). The reasons for initial dose reductions were patients’ age (>75 years) in seven cases, bloody sputum in three, and other general conditions in three. The median duration of lenvatinib treatment was 13.5 months (range, 2.1–89.9). The distributions of the relative dose intensity separated by 10% are shown in Fig. 1. The reasons for treatment discontinuation were disease progression in 15 patients and adverse events in five. The mean and median dose intensities of lenvatinib during the whole treatment were 11.2 mg/day (SD = 4.4) and 9.9 mg/day (range, 4.3–23.9), respectively. The mean and median 8 weeks’ dose intensities were 15.8 mg/day (SD = 4.5) and 16.1 mg/day (range, 5.5–24.0), respectively. The dose intensity of lenvatinib during the whole treatment period was negatively correlated with the duration of lenvatinib treatment ($r_c = -0.47, p < 0.002$).

### Table 1  Patients’ characteristics

| Characteristics                                      | N = 42 |
|------------------------------------------------------|--------|
| Age (years), median (range)                          | 69 (22–83) |
| Sex, n (%)                                           |        |
| Male                                                 | 16 (38.1%) |
| Female                                               | 26 (61.9%) |
| Histological subtype, n (%)                          |        |
| Papillary thyroid cancer                              | 38 (90.5%) |
| Follicular thyroid cancer                             | 4 (9.5%) |
| ECOG PS, n (%)                                       |        |
| 0                                                     | 18 (42.9%) |
| 1                                                     | 24 (57.1%) |
| Tumor-related symptom, n (%)                         | 13 (31.0%) |
| Metastatic sites, n (%)                               |        |
| Lung                                                  | 37 (88.1%) |
| Lymph node                                            | 22 (52.4%) |
| Bone                                                  | 8 (19.1%) |
| Liver                                                 | 4 (9.5%) |
| Prior surgery, n (%)                                  | 42 (100.0%) |
| Mean cumulative dose of iodine-131 therapy, mCi (SD)  | 155.7 (102.7) |
| Prior chemotherapy, n (%)                             |        |
| Sorafenib                                             | 4 (9.5%) |
| Vandetanib                                            | 1 (2.4%) |
| Thyroglobulin doubling time (years), median (range)   | 0.79 (–0.38–21.88) |
| Neutrophil-to-lymphocyte ratio, median (range)        | 2.52 (1.35–6.95) |
| Sum of diameters of target lesions (mm), median (range)| 41.1 (15.5–112.0) |
| Diameters of maximum target lesion (mm), median (range)| 23.5 (12.3–81.6) |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

8w-RDI as a marker of lenvatinib for DTC
**Relationship between treatment outcomes and dose intensity**

The ORR and DCR were 73.8% and 97.6%, respectively. The median PFS and OS rates were 20.2 months (range, 10.6–not reached [NR]) and 35.2 months (range, 23.1–NR), respectively.

There was no significant difference in PFS between patients with a higher dose intensity during the whole treatment period (defined as higher than the median of 9.9 mg/day) and patients with a lower dose intensity than the median (20.3 vs. 22.5 months; HR 1.15; 95% CI 0.46–2.85; \( p = 0.76 \)). The receiver operating characteristic (ROC) curve of 8w-RDI was analyzed, and the objective response was predicted by comparing the AUC. We determined that the best cut-off value for 8w-RDI was 60.0% (sensitivity: 81.8%; specificity: 80.6%; AUC of the ROC curve: 0.83). Patients with a higher 8w-RDI (≥60% [14.4 mg/day]) had better PFS compared with patients with a lower 8w-RDI (<60%) (NR vs. 11.0 months; HR 0.29; 95% CI 0.11–0.72; \( p < 0.01 \)) (Fig. 2A). Similar results were observed for OS (NR vs. 27.6 months; HR 0.31; 95% CI 0.11–0.91; \( p = 0.03 \)) (Fig. 2B). Landmark survival analysis at 8 weeks for PFS and OS are shown in Supplementary Fig. 1. Patients with a higher 8w-RDI had a significantly better ORR than patients with a lower 8w-RDI (92.3% vs. 43.8%; \( p < 0.001 \)). The median time to the first CT evaluation was 2.8 months (range, 1.9–7.6), and the median DpR at the first CT evaluation was 33.5% (range, 2.4–48.9). The median DpR at the first CT evaluation was 35.1% in the higher 8w-RDI group and 21.6% in the lower 8w-RDI group (\( p < 0.01 \)), and the DpR at the first CT evaluation was modestly correlated with 8w-RDI (\( r = 0.37; p < 0.02 \)) (Fig. 3).

**Factors affecting 8w-RDI**

We compared several patient parameters that might affect 8w-RDI between patients with a higher or lower 8w-RDI (Table 2). There were no significant differences in age, sex, histology, ECOG PS, pretreatment serum albumin level, estimated glomerular filtration rate, and comorbidities between patients with a higher or lower 8w-RDI.
During the first 8 weeks after lenvatinib induction, dose reductions were performed 56 times among the patient cohort. The most frequent reasons for dose reduction were proteinuria in 14 (25.0%) events, hypertension in 11 (19.6%), palmar-plantar erythrodysesthesia syndrome in nine (16.1%), fatigue in four (7.1%), anorexia in three (5.4%), and bleeding in three (5.4%).

**Multivariate analysis for PFS and OS**

The multivariate analysis of predictive factors for PFS is presented in Table 3. In this analysis, 8w-RDI ≥60% was an independent prognostic factor for PFS (HR 0.29; 95% CI 0.09–0.96; p = 0.04). A similar non-significant trend was also observed in OS (HR 0.28; 95% CI 0.06–1.23; p = 0.09).

**Discussion**

We investigated the dose intensity of lenvatinib for patients with RR-DTC to visualize the relationship between the dose intensity of lenvatinib and treatment.

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**Table 2** Comparison of patients’ characteristics according to 8 weeks’ relative dose intensity

| Characteristics                              | 8w-RDI ≥60% | 8w-RDI <60% | p-value |
|----------------------------------------------|-------------|-------------|---------|
| Age (years), median (range)                  | N = 26      | N = 16      |         |
| Sex, n (%)                                   |             |             | 1.00    |
| Male                                         | 10 (38.5%)  | 6 (62.5%)   |         |
| Female                                       | 16 (61.5%)  | 10 (37.5%)  |         |
| Histological subtype, n (%)                  |             |             | 1.00    |
| Papillary thyroid cancer                     | 23 (88.5%)  | 15 (93.8%)  |         |
| Follicular thyroid cancer                    | 3 (11.5%)   | 1 (6.2%)    |         |
| ECOG PS, n (%)                               |             |             |         |
| 0                                            | 14 (53.8%)  | 4 (25.0%)   |         |
| 1                                            | 12 (46.2%)  | 12 (75.0%)  |         |
| Tumor-related symptom, n (%)                 |             |             | 1.00    |
| Mean cumulative dose of iodine-131 therapy, mCi (SD) | 100 (27–450) | 200 (30–380) | .45     |
| Thyroglobulin doubling time (years), median (range) | 0.91 (0.13–21.9) | 0.46 (–0.38–7.14) | .18  |
| Sum of diameters of target lesions (mm), median (range) | 40.0 (16.3–74.0) | 41.8 (15.5–112.0) | .53 |  |
| Diameters of maximum target lesion (mm), median (range) | 22.4 (12.9–50.0) | 25.7 (12.3–81.6) | .89 |  |
| Serum albumin level (g/dL), median (range)   | 4.1 (3.3–4.7) | 4.0 (3.0–4.4) | .30     |
| eGFR (mL/min/1.73 m²), median (range)        | 80.5 (41.3–132.40) | 73.5 (47.5–126.70) | .26 |

Abbreviations: 8w-RDI, 8 weeks’ relative dose intensity; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; eGFR, estimated glomerular filtration rate
outcomes. Our results demonstrated that the dose intensity of lenvatinib during the first 8 weeks of treatment was associated with treatment response and PFS, and it was further validated as an independent prognostic factor for PFS in the multivariate analysis.

At present, lenvatinib is a standard therapy for unresectable or metastatic RR-DTC patients, based on the high ORR and prolonged PFS reported in the SELECT trial. However, lenvatinib has a relatively high incidence of adverse events, with more than 80% of patients experiencing grade ≥3 adverse events in the SELECT trial [4, 6]. Although the importance of avoiding longer (≥10%) treatment interruption has been reported, it is not easy to maintain the dose intensity of lenvatinib because of the associated adverse events. In addition, it was reported that tumor shrinkage by lenvatinib is the greatest during the first 8 weeks, though the required dose intensity to yield a good treatment response has not been established. Our results provide a possible standard for the target dose intensity of lenvatinib during the first 8 weeks.

The backgrounds of patients with higher or lower RDIs were not particularly different, indicating that it is difficult to predict the development of treatment-related adverse events before lenvatinib administration according to the patient’s background. Therefore, physicians should appropriately treat any adverse events to enable the continuation of lenvatinib. Several adverse events of lenvatinib have specific treatment approaches, for example, antihypertensive drugs for hypertension, topical corticosteroids and urea-based cream for palmar-plantar erythrodysesthesia syndrome, and antiemetics for nausea [11]. However, these toxicities cannot always be controlled despite the availability of appropriate supportive therapies. In fact, hypertension and palmar-plantar erythrodysesthesia syndrome were the second and third most frequent reasons for dose reduction during the first 8 weeks of treatment in the present study. In addition, several adverse events of lenvatinib (e.g., proteinuria, fatigue, and anorexia) do not have a specific treatment. To relieve these adverse events, dose interruption and dose reduction of lenvatinib are required in most cases.

Very severe adverse events can lead to treatment discontinuation. To avoid severe or intolerable adverse

| Table 3 | Multivariate analysis of progression-free survival and overall survival |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|
|         | Progression-free survival | Overall survival |
|         | HR    | 95% CI    | p-value | HR    | 95% CI    | p-value |
| Age     |       |           |         |       |           |         |
| <65 years | Reference | 1.17 | 0.39–3.59 | .78 | Reference | 2.54 | 0.60–10.68 | .20 |
| ≥65 years |         |          |         |       |          |         |
| Sex     |       |           |         |       |           |         |
| Male    | Reference | 0.68 | 0.19–2.33 | .54 | Reference | 0.74 | 0.17–3.34 | .70 |
| Female  |         |           |         |       |          |         |
| ECOG PS |       |           |         |       |           |         |
| 0       | Reference | 1.63 | 0.50–5.32 | .41 | Reference | 0.81 | 0.16–4.14 | .80 |
| 1       |         |           |         |       |          |         |
| Tumor-related symptom |       |           |         |       |           |         |
| No      | Reference | 0.58 | 0.15–2.31 | .44 | Reference | 1.00 | 0.21–4.70 | 1.00 |
| Yes     |         |           |         |       |          |         |
| Thyroglobulin doubling time |       |           |         |       |           |         |
| <1 years | Reference | 0.53 | 0.15–1.90 | .33 | Reference | 0.92 | 0.18–4.76 | .92 |
| ≥1 years |         |           |         |       |          |         |
| Bone metastasis |       |           |         |       |           |         |
| No      | Reference | 2.26 | 0.52–9.83 | .28 | Reference | 1.04 | 0.18–5.92 | .97 |
| Yes     |         |           |         |       |          |         |
| 8w-RDI (%) |       |           |         |       |           |         |
| <60%    | Reference | 0.29 | 0.09–0.96 | .04 | Reference | 0.28 | 0.06–1.23 | .09 |
| ≥60%    |         |           |         |       |          |         |

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; 8w-RDI, 8 weeks’ relative dose intensity.
events, the effectiveness of planned drug holidays of lenvatinib has been reported [12]. One frequently used method is a 1-week-off approach. In this method, lenvatinib is withdrawn before the occurrence of severe or intolerable adverse events and is restarted after 1 week if the toxicity has recovered. When 24 mg lenvatinib is administered according to the 2-weeks-on/1-week-off method, the RDI for these 3 weeks is 66.7%. Another option is the weekends-off method. In the treatment of hepatocellular carcinoma (HCC), 5-days-on/2-days-off administration of lenvatinib improved tolerability and significantly prolonged treatment duration and overall survival [13]. Although the maximum dose of lenvatinib for HCC (12 mg/day) is lower than that for thyroid cancer (24 mg/day) [14], this 5-days-on/2-days-off method can be an option for the treatment of thyroid cancer patients, especially for those who cannot continue lenvatinib for more than 1 week because of adverse events. When 24 mg lenvatinib is administered according to the 5-days-on/2-days-off method, the RDI is 71.4%. These are possible methods that can achieve ≥60% of the 8w-RDI. Dose reductions of lenvatinib are also essential to control adverse events and enable treatment continuation. The dose levels of lenvatinib were 24, 20, 14, 10, and 8 mg/day in the SELECT trial, and dose is reduced in accordance with this protocol in current clinical practice. Thus, 60% of 8w-RDI is equivalent to 14.4 mg/day of dose intensity. This indicates it is difficult to achieve 60% of 8w-RDI when the dose of lenvatinib is reduced to less than 14 mg/day in the early phase of the treatment. Most recently, in Study 211, a randomized phase 2 study, 18 mg/day lenvatinib starting dose did not show non-inferiority to 24 mg/day in terms of ORR [15, 16]. It is reported that dose reduction and interruption is required even in patients who started lenvatinib at a reduced dose [17]. Taking these results together, it might be insufficient to achieve ≥60% of 8w-RDI when starting lenvatinib at a reduced dose because of adverse events. In the present study, 13 patients who started lenvatinib at a reduced dose (≤20 mg/day) had a slightly lower median 8w-RDI (63.5% vs. 69.3%; \(p = 0.29\)) and a shorter median PFS (11.0 months vs. 34.7 months; \(p = 0.07\)) than patients who started lenvatinib at 24 mg, though this finding was not significant. Moreover, the median PFS (NR vs. 15.9 months; HR 0.29; 95% CI 0.11–0.72; \(p < 0.02\)) was longer in higher 8w-RDI group for 29 patients who started lenvatinib at 24 mg than lower 8w-RDI group. Therefore, these results indicate that the optimal starting dose of lenvatinib is still 24 mg/day if possible, and dose reduction and dose interruption, including planned drug holidays, should be performed targeting for ≥60% of 8w-RDI to achieve a high ORR and prolonged PFS.

The median PFS in the present study was 20.2 months, which was longer than that reported in the SELECT trial (18.3 months). This is because we excluded patients who could not continue lenvatinib for more than 8 weeks. Indeed, the median PFS and OS for the excluded seven patients who could not continue lenvatinib for 8 weeks were 1.9 months and 4.0 months, respectively, and all of these patients died of disease. The sum of the target lesions was greater in the excluded seven patients (84.5 mm [range, 44.5–109.0]) than in the enrolled 42 patients (41.1 mm [range, 15.5–112.0]), though other characteristics, including age, sex, and ECOG PS, were not different. Several previous reports described that pretreatment tumor volume can be a negative prognostic factor [18, 19]. Patients who could not continue lenvatinib for 8 weeks might have had greater tumor burden, and thus the disease activity could not be controlled by lenvatinib.

Our results showed negative correlation between dose intensity during the whole treatment period and the treatment duration. One possible explanation is that the patients with lower dose intensity during the whole treatment period might experience more adverse events than patients with higher dose intensity. It is reported that occurrence of some adverse events such as hypertension, can be associated with prolonged survival in the SELECT trial [20]. Indeed, the incidence is slightly higher in patients with higher 8w-RDI than those with lower 8w-RDI in our results. Another possible explanation is that patients with lower dose intensity were more likely to be reduced or interrupted lenvatinib dose due to adverse events, thus allowing them to continue lenvatinib for a longer treatment duration.

The present study has several limitations. The number of patients was relatively small. Furthermore, the retrospective design at a single institute is an obvious limitation. Because the patients were treated in daily clinical settings, the treatment procedures (e.g., the frequency of patients’ visits, the timing of CT evaluations, and the protocol of dose modifications) were not standardized. In addition, we excluded patients who were unable to continue lenvatinib for more than 8 weeks, and the present study could not indicate how these patients could be salvaged. Although we set the cut-off period of RDI at 8 weeks, the optimal cut-off period is not exactly established. We exploratory performed similar analysis for 4 weeks’ RDI (4w-RDI). The best cut-off value for 4w-RDI was 71.5% (sensitivity: 81.8%; specificity: 93.5%; AUC of the ROC curve: 0.84). Patients with a higher 4w-RDI (≥71.5%) had better PFS compared with patients with a lower 4w-RDI (<71.5%) (34.7 vs. 10.6 months; HR 0.33; 95% CI 0.13–0.80; \(p < 0.03\)), however, the median OS was identical between higher and lower 4w-RDI patients (35.0 vs. 35.2 months; HR 0.49;
95% CI 0.18–1.32; p = 0.16) (Supplementary Fig. 2). RDI at 4 weeks might be too early to predict long-term outcomes of lenvatinib treatment. Nonetheless, while we cannot suggest the precise factors and methods that are essential for maintaining 8w-RDI at ≥60%, we can propose that the target 8w-RDI might be enough at ≥60%.

In conclusion, we identified that an 8w-RDI of not less than 60% was an independent predictor for PFS in RR-DTC patients treated with lenvatinib. Administration of a sufficient dose of lenvatinib for the first 8 weeks is essential to achieve significant tumor shrinkage and prolong PFS, and targeting for ≥60% of 8w-RDI is adequate. These findings should be validated in a larger prospective investigation.

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**Disclosure**

None of the authors have any potential conflicts of interest associated with this research.

**References**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68: 394–424.

2. Scuito R, Romano I, Rea S, Marandino F, Sperduti I, et al. (2009) Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. *Ann Oncol* 20: 1728–1735.

3. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, et al. (2006) Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radiodine therapy. *J Clin Endocrinol Metab* 91: 2892–2899.

4. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, et al. (2015) Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 372: 621–630.

5. Tahara M, Brose MS, Wirth LJ, Suzuki H, Niizeki T, Nakano M, et al. (2017) Optimal use of lenvatinib in the treatment of advanced thyroid cancer. *Cancers (Basel)* 9: 1010.

6. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, et al. (2018) Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 391: 1163–1173.

7. ClinicalTrials.gov. A Phase 2 Trial of Lenvatinib (E7080) in Subjects With Iodine-131 Refractory Differentiated Thyroid Cancer to Evaluate Whether an Oral Starting Dose of 18 mg Daily Will Provide Comparable Efficacy to a 24 mg Starting Dose, But Have a Better Safety Profile. https://clinicaltrials.gov/ct2/show/NCT02702388 accessed on November 12, 2020.

8. Robinson B, Schlumberger M, Wirth LJ, Dutcus CE, Song J, et al. (2016) Characterization of tumor size changes over time from the phase 3 study of lenvatinib in thyroid cancer. *J Clin Endocrinol Metab* 101: 4103–4109.

9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228–247.

10. Kanda Y (2013) Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. *Bone Marrow Transplant* 48: 452–458.

11. Takahashi S, Kiyota N, Tahara M (2017) Optimal use of lenvatinib in the treatment of advanced thyroid cancer. *Cancers (Basel)* 9: 1010.
Hughes BGM, et al. (2020) A multicenter, randomized, double-blind, phase II study of lenvatinib (LEN) in patients (pts) with radioiodine-refractory differentiated thyroid cancer (RR-DTC) to evaluate the safety and efficacy of a daily oral starting dose of 18 mg vs. 24 mg. ESMO Asia Virtual Congress 2020, 426P (abstract)

17. Yamazaki H, Iwasaki H, Takasaki H, Suganuma N, Sakai R, et al. (2019) Efficacy and tolerability of initial low-dose lenvatinib to treat differentiated thyroid cancer. *Medicine (Baltimore)* 98: e14774.

18. Suzuki C, Kiyota N, Imamura Y, Goto H, Suto H, et al. (2019) Exploratory analysis of prognostic factors for lenvatinib in radioiodine-refractory differentiated thyroid cancer. *Head Neck* 41: 3023–3032.

19. Tahara M, Kiyota N, Hoff AO, Badiu C, Owonikoko TK, et al. (2019) Impact of lung metastasis on overall survival (OS) in the phase III SELECT study with lenvatinib (LEN) in patients (pts) with radioiodine refractory differentiated thyroid cancer (RR-DTC). Abstract Book of the 44th ESMO Congress (ESMO 2019), 1862PD (abstract)

20. Wirth LJ, Tahara M, Robinson B, Francis S, Brose MS, et al. (2018) Treatment-emergent hypertension and efficacy in the phase 3 Study of (E7080) lenvatinib in differentiated cancer of the thyroid (SELECT). *Cancer* 124: 2365–2372.