Research Square

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# Impact of a Weekend-Off Lenvatinib Dosing Regimen on Dose Intensity and Safety in Lenvatinib–Pembrolizumab Therapy for Advanced Endometrial Cancer

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# Abstract

**Background:** Lenvatinib plus pembrolizumab (LP) therapy improves survival in patients with advanced or recurrent endometrial cancer; however, treatment-related toxicities frequently necessitate dose modification or interruption. Maintaining the lenvatinib relative dose intensity (RDI) may influence therapeutic outcomes. The aim of this study was to evaluate the RDI and safety of a weekend-off lenvatinib dosing regimen within LP therapy.

**Methods:** This retrospective study included 56 patients with advanced or recurrent endometrial cancer treated with LP therapy at three Japanese institutions between December 2021 and March 2024. Fifteen patients received a weekend-off regimen and 41 received conventional daily dosing. The lenvatinib RDI was calculated at 6 and 9 weeks. Adverse events (AEs) were compared between the two groups.

**Results:** Lenvatinib RDI at 6 and 9 weeks tended to be higher in the weekend-off group than in the conventional group, although the difference was not significant (6-week: median 73.1% vs. 61.0%, p = 0.361; 9-week: median 72.5% vs. 58.3%, p = 0.202). Despite this trend toward higher dose intensity, grade ≥3 AEs were significantly less frequent in the weekend-off group than in the conventional group (46.7% vs. 80.5%; p = 0.0203).

**Conclusions:** The weekend-off lenvatinib regimen maintained an RDI comparable to, and in some cases higher than, conventional daily dosing, while significantly reducing severe toxicities. These findings support the feasibility of a weekend-off schedule as a strategy for improving the tolerability of LP therapy without compromising dose intensity.


# INTRODUCTION

The global incidence of endometrial cancer continues to rise [1], with approximately 417,000 new cases and 97,000 deaths reported in 2020 [2]. The overall 5-year survival rate is 81.3%, and most early stage (International Federation of Gynecology and Obstetrics (FIGO) stages I–II) cases achieve favorable outcomes with surgery and adjuvant therapy. In contrast, patients with recurrent or metastatic disease have a poor prognosis, with a 5-year survival rate of less than 30% and limited treatment options [3, 4].

The Phase 3 KEYNOTE-775 trial demonstrated that lenvatinib plus pembrolizumab (LP) therapy significantly improved overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone in advanced or recurrent endometrial cancer, establishing LP therapy as a key second-line treatment [5]. LP therapy has been reported to be effective in clinical settings [6]. However, the regimen is associated with substantial toxicity; in KEYNOTE-775, grade ≥ 3 adverse events were frequent, leading to treatment interruption in 69.2% of patients, dose reduction in 66.5%, and discontinuation in 33% [5]. These findings underscore a major clinical challenge: balancing tolerability against the need to maintain an adequate lenvatinib relative dose intensity (RDI), which may influence treatment efficacy.

Prior studies in thyroid and liver cancer have shown that maintaining higher RDI improves survival outcomes, and that a 5-days-on/2-days-off "weekend-off" regimen can enhance tolerability while preserving RDI [7–9]. Due to the high toxicity of LP therapy and the potential impact of RDI on clinical outcomes, optimizing the balance between safety and dose intensity is an urgent clinical priority. Therefore, we conducted a multicenter retrospective study to evaluate whether a weekend-off lenvatinib regimen could maintain the RDI and improve tolerability compared with the conventional daily dosing schedule.

# PATIENTS AND METHODS

## Study Design and Patients

This retrospective study was approved by the Ethics Committee of Iwate Medical University School of Medicine and conducted in accordance with the Declaration of Helsinki (ethical code: 18146). We evaluated 66 patients with recurrent or advanced endometrial cancer who underwent LP therapy at three Japanese institutions (Iwate Medical University, Kindai University, and Kumamoto University) between December 2021 and March 2024. Ten patients were excluded due to missing or incorrect data. Therefore, 56 patients were included in the final analysis.

The patients were classified into two groups based on the treatment protocol used at the time of treatment initiation. The weekend-off protocol was implemented at all three institutions in April 2023. Patients treated before April 2023 were assigned to the conventional group (n = 41), whereas those treated from April 2023 onward were assigned to the weekend-off group (n = 15). The weekend-off regimen was introduced as a protocol-level dose modification strategy to improve tolerability, primarily in response to the high frequency of treatment-related toxicities observed with conventional daily dosing (Supplemental Fig. 1).

## Treatment Protocol

All patients were treated with intravenous pembrolizumab 200 mg every three weeks and oral lenvatinib 20 mg daily. The weekend-off regimen consisted of a cycle of five consecutive days of lenvatinib administration followed by two consecutive days off (Saturday and Sunday). For patients who developed unacceptable lenvatinib-related adverse events (AEs) (i.e., grade ≥ 3), the dose of lenvatinib was reduced or administration was temporarily interrupted until the AEs improved to grade ≤ 2. Dose reduction was performed according to manufacturer's recommendations. The treatment protocol is presented in Fig. 1.

## Efficacy and Safety Evaluation

Treatment efficacy was evaluated using computed tomography (CT) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [10]. The severity of AEs was assessed using the

Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0-JCOG) developed by the Japan Clinical Oncology Group [11].

PFS was defined as the time from treatment initiation to disease progression or death from any cause, whichever occurred first. Patients without adverse events were censored at the date of their last follow-up. Given the retrospective design and limited sample size, PFS was analyzed as an exploratory endpoint and interpreted for hypothesis generation.

Because pembrolizumab was administered every 3 weeks, lenvatinib RDI was evaluated at 6 and 9 weeks with planned cumulative doses of 840 mg and 1,260 mg, respectively. The RDI was calculated as the ratio of the actual dose to the planned cumulative dose and expressed as a percentage.

# Statistical Analysis

GraphPad Prism version 10.0 (GraphPad Software, San Diego, CA, USA) was used to generate graphs and perform statistical analyses. Continuous variables were compared between groups using the Mann–Whitney U test, and categorical variables were compared using Fisher's exact test. Percentages and two-sided 95% confidence intervals (CI; Clopper–Pearson method) were calculated for the objective response rate (ORR) and disease control rate (DCR). PFS was estimated using the Kaplan–Meier method and compared using the log-rank test. To identify factors independently associated with PFS, univariate Cox proportional hazards analysis was first performed for each clinical variable. Variables with $p < 0.05$ in univariate analysis, along with clinically relevant factors (age, Eastern Cooperative Oncology Group (ECOG) performance status, histological subtype, mismatch repair (MMR) status, and number of prior treatment regimens), were subsequently included in the multivariate Cox proportional hazards model. The association between lenvatinib RDI and PFS was also evaluated using Cox proportional hazards regression, with lenvatinib RDI treated as a continuous variable in all Cox regression analyses. Statistical significance was defined as a two-sided p-value < 0.05.

## RESULTS

# Patient Characteristics

The patient characteristics are shown in Table 1. A total of 56 patients received LP therapy between December 2021 and March 2024, with 15 and 41 patients in the weekend-off and conventional groups, respectively. There were no statistically significant differences between the two groups in terms of age, body mass index, ECOG performance status, histological subtype, or number of prior treatment regimens. The median age was 64 y in both groups (range, 41–80). All patients had ECOG performance status scores of 0 or 1. The histological subtypes included endometrioid carcinoma, serous carcinoma, carcinosarcoma, and dedifferentiated carcinoma. The median number of prior treatment regimens was 1.5 in the conventional group and 1 in the weekend-off group. Regarding MMR status, proficient MMR (pMMR) was observed in 33 patients (80.5%) in the conventional group and in seven patients (46.7%) in

the weekend-off group. The deficient MMR (dMMR) rate (= dMMR / (dMMR + pMMR)) was 15.4% in the conventional group and 30% in the weekend-off group (p = 0.364). The median treatment-free interval was 328.5 d (range, 27–2,027) in the weekend-off group and 104.5 d (range, 1–1,867) in the conventional group.

Table 1
Patients' characteristics

| **Age, median(range)** | **Weekend-off group(n = 15)** | **Conventional group(n = 41)** | **P value** |
|---|---|---|---|
| | **64(49–80)** | **64(41–79)** | **0.853** |
| BMI, median(range) | 25.6(17.8–42.3) | 23.2(15.1–35.0) | 0.56 |
| ECOG PS(%) | | | 0.120 |
| 0 | 12(80.0) | 22(53.7) | |
| 1 | 3(20.0) | 19(46.3) | |
| Histology (%) | | | 0.562 |
| Endmetrioid carcinoma | 8(53.3) | 24(58.5) | |
| Grade1 | 7(46.7) | 16(39.0) | |
| Grade2 | 0 | 4(9.8) | |
| Grade3 | 1(6.7) | 4(9.8) | |
| Serous carcinoma | 2(13.3) | 2(4.9) | |
| Carcinosarcoma | 2(13.3) | 10(24.4) | |
| Dedifferentiated carcinoma | 1(6.7) | 2(4.9) | |
| Others | 2(13.3) | 3(7.3) | |
| Number of prior treatment regimens (median) | 1 | 1.5 | 0.09 |
| FIGO stage(%) | | | 0.543 |
| □-□ | 4(26.7) | 15(36.6) | |
| □-□ | 11(73.3) | 26(63.4) | |
| MMR status | | | 0.00284 |
| pMMR | 7(46.7) | 33(80.5) | |
| dMMR | 3(53.3) | 6(19.5) | |
| unknown | 5 | 2 | |
| TFI, median(range) | 328.5(27-2027) | 104.5(1-1867) | 0.177 |

ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, the International Federation of Gynecology and Obstetrics; MMR, mismatch repair; pMMR, MMR-proficient; dMMR, MMR-deficient.

## Clinical Benefit

The lenvatinib RDI was compared between the two groups at 6 and 9 weeks (Fig. 2). The median RDI was higher in the weekend-off group at both time points (6 weeks: 73.1% vs. 61.0%, p = 0.361; 9 weeks: 72.5% vs. 58.3%, p = 0.202).

Because of the imbalance in the MMR status between the groups and the short follow-up period, an exploratory analysis was performed to assess the clinical benefits. The Kaplan–Meier estimates of PFS did not differ significantly between the two groups (p = 0.6898; HR, 1.191; 95% CI, 0.5045–2.813; Fig. 3). The ORR was higher in the weekend-off group (66.7% vs. 56.1%, p = 0.551).

In the multivariate Cox proportional hazards model, an ECOG performance status of 0 was independently associated with improved PFS (HR, 2.254; 95% CI, 1.148–4.426) (Table 2).

Table 2
Prognostic Factors Associated with PFS in Lenvatinib Plus Pembrolizumab Therapy

| **Factors** | **univariate analysis** | | | **multivariate analysis** | | |
|---|---|---|---|---|---|---|
| | **HR** | **95%CI** | **p value** | **HR** | **95%CI** | **p value** |
| Age | 0.9674 | 0.9241–1.013 | 0.1565 | 0.6935 | 0.2405-2.000 | 0.4981 |
| ECOG PS(0/1) | 2.254 | 1.148–4.426 | 0.01825 | 2.391 | 1.1510–4.969 | 0.0195 |
| FIGO Stage(□-□/□-□) | 1.043 | 0.8205–1.326 | 0.731 | 1.009 | 0.7913–1.286 | 0.9429 |
| Histlogical type<br>(EM G1-2/non-EM G1-2) | 1.718215 | 0.8661–3.409 | 0.1215 | 1.569 | 0.7864–3.129 | 0.2013 |
| MMR status<br>(pMMR or dMMR/unkwown) | 1.304 | 0.5992-2.84 | 0.5031 | 1.192 | 0.4892–2.903 | 0.6996 |
| weekend-off/conventional | 0.8395 | 0.3555–1.982 | 0.6898 | 0.5856 | 0.2344–1.463 | 0.2521 |

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EMG1-2, Grade 1–2 endometrioid carcinoma; FIGO, International Federation of Gynecology and Obstetrics; MMR, mismatch repair; pMMR, MMR-proficient; dMMR, MMR-deficient.

## Safety

All the patients experienced grade 1 or higher AEs. The most frequent AE was fatigue (conventional group: 71.4%; weekend-off group: 63.1%). Dose reduction due to AEs was required in 75.6% (n = 31) of the patients in the conventional group and in 31.6% (n = 6) of the patients in the weekend-off group. Lenvatinib interruption was required in 97.6% (n = 40) of the patients in the conventional group and 100% of the patients in the weekend-off group.

The most frequent grade ≥ 3 AEs requiring lenvatinib dose modification were hypertension (conventional group: 19.5%; weekend-off group: 13.3%), proteinuria (conventional group: 14.6%; weekend-off group: 13.3%), and fatigue (conventional group: 13.3%; weekend-off group: 6.7%). The overall incidence of grade ≥ 3 AEs was 80.5% (n = 33) in the conventional group and 46.7% (n = 7) in the weekend-off group (Fig. 4).

The incidence of grade ≥ 3 AEs was significantly lower in the weekend-off group (p = 0.0203) (Fig. 4). No significant difference in the incidence of grade ≥ 3 AEs was observed between patients with ≤ 1 prior treatment regimens and those with ≥ 2 prior regimens (p = 1.0). Treatment discontinuation due to AEs occurred in 39.0% (n = 16) of the patients in the conventional group and in 20.0% (n = 3) of the patients in the weekend-off group. One treatment-related death occurred owing to pembrolizumab-induced immune-related pneumonitis.

# DISCUSSION

In the KEYNOTE-158 trial, pembrolizumab monotherapy demonstrated efficacy in treating advanced or recurrent endometrial cancer with high microsatellite instability, although early progression was observed within the first three months [12, 13]. As approximately 80% of endometrial cancers are pMMR and immune checkpoint inhibitors have limited efficacy as monotherapy in this population [14], the KEYNOTE-775 trial investigated the efficacy of adding lenvatinib to the treatment regimen. Results showed that this combination significantly improved early disease control and prolonged PFS [5]. These findings suggested that lenvatinib is crucial for enhancing the efficacy of pembrolizumab in most cases of endometrial cancer. Our analysis further suggests that maintaining early lenvatinib exposure through a weekend-off dosing strategy may improve the tolerability and treatment continuity of LP therapy.

LP therapy is often limited by treatment-related toxicity, which makes sustained administration one of the most significant clinical challenges associated with this regimen. Therefore, effective management of toxicity is essential to enable patients to continue treatment and maintain adequate lenvatinib exposure. To our knowledge, this is the first study to evaluate the feasibility and clinical utility of a weekend-off lenvatinib regimen in the context of LP therapy for endometrial cancer.

The most notable finding in this study was that the weekend-off regimen significantly reduced the incidence of grade ≥ 3 AEs. As lenvatinib is an oral agent frequently associated with intolerable toxicities, optimization of dosing strategies to improve tolerability while maintaining sufficient dose intensity is essential for treatment continuity. Notably, this reduction in severe toxicity was achieved despite an RDI that was not significantly different from, and tended to be higher than, that observed in the conventional

group. These results suggest that a weekend-off regimen may represent a feasible approach for balancing tolerability and the maintenance of treatment exposure. Previous studies in thyroid cancer have shown that maintaining an 8-week RDI of at least 60% is associated with improved PFS and greater tumor shrinkage (HR, 0.29; 95% CI, 0.11–0.72; $p < 0.01$) [7], supporting the prognostic importance of sustained dose intensity. Furthermore, studies on hepatocellular carcinoma (HCC) have shown that compared to dose reduction, a weekend-off (5 days on, 2 days off) regimen better preserves RDI and tolerability [8, 9]. Importantly, the two strategies differ in the drug exposure they achieve relative to their dose intensity. Pharmacokinetic modeling has shown that the 12-mg weekend-off regimen maintains an area under the curve (AUC) of approximately 70% of continuous daily dosing, which closely matches its RDI (~ 71%), whereas an 8-mg reduced-dose schedule yields an AUC of only approximately 45%, well below the corresponding RDI (~ 67%) [8]. Thus, dose reduction lowers systemic exposure disproportionately to the reduction in dose intensity, whereas weekend-off dosing preserves exposure roughly in proportion to it. Given that lenvatinib has a plasma half-life of approximately 28 h [15], a 2-day interruption may alleviate cumulative toxicities such as fatigue and improve patient adherence.

Consistent with previous HCC data, our study demonstrated that the weekend-off group experienced fewer severe AEs, including hypertension and fatigue, supporting its potential as a well-tolerated and feasible strategy to maintain therapeutic exposure [8]. However, several challenges remain to be resolved. In particular, grade ≥ 3 AEs, such as thrombocytopenia, tended to be more frequent in the weekend-off group, indicating that myelosuppression may not be fully resolved within a 2-day rest period.

This study had some limitations. First, as a retrospective study with a historical control design, it was subject to unmeasured confounding factors, and contemporaneous changes in patient characteristics, supportive care, and treatment strategies may have influenced the results. Second, a formal between-group comparison of PFS was not performed because of three factors that together precluded a reliable efficacy assessment: a substantial imbalance in MMR status (dMMR rate: 15.4% vs. 30.0%), a small sample size, particularly in the weekend-off group ($n = 15$), and a short follow-up period, which was insufficient to capture long-term outcomes and delayed toxicities. Therefore, long-term efficacy requires validation in future prospective multicenter studies. Third, minor AEs may have been underestimated due to real-world limitations in clinical documentation. To confirm the benefits of an intermittent dosing strategy and to identify which patients would benefit the most, a prospective, multicenter study with longer-term follow-up is warranted.

# Conclusion

In this multicenter retrospective study, the weekend-off lenvatinib regimen maintained an RDI comparable to, and numerically higher than, that achieved with conventional daily dosing, while significantly reducing the incidence of grade ≥ 3 AEs. Therefore, the weekend-off administration of LP therapy may be a feasible regimen with improved tolerability in patients with advanced or recurrent

endometrial cancer. Further validation through prospective multicenter studies with long-term follow-up is warranted.

# Declarations


### Acknowledgements

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### Funding

This research received no external funding.


### Conflict of Interest

Dr. M. K. has received lecture fees from Merck Sharp & Dohme and Eisai and has served on an advisory board for Merck Sharp & Dohme. Dr. N. M. received research grants from AstraZeneca and Eisai, and lecture fees from Merck Sharp & Dohme, AstraZeneca, and Takeda Pharmaceutical Company. Dr. T. B. received research grants from Merck Sharp and Dohme and lecture fees from Merck Sharp, Dohme, and Eisai. The authors declare no conflicts of interest.

### Ethics Approval

This study was conducted in accordance with the ethical standards of the institutional and national research committees and the 1964 Helsinki Declaration and its later amendments. Ethical approval was obtained from the Iwate Medical University Ethics Committee (Approval No. 18146), as well as from the ethics committees of Kinki University and Kumamoto University.

### Informed Consent

Given the retrospective nature of this study and the use of anonymized clinical data, the requirement for written informed consent was waived by the respective institutional review boards. An opt-out procedure was implemented at each institution in accordance with the national guidelines.

### Data Availability

The datasets generated and analyzed during the current study are not publicly available due to institutional policies on patient confidentiality, but are available from the corresponding author upon reasonable request.

**Author Contributions** (CRediT taxonomy)

- Conceptualization: N.M.
- Methodology: M.K., E.K., N.M., T.B.
- Formal analysis: N.J., M.K.

- Investigation: N.J., N.A., M.K., H.S., S.T., Y.C., S.S., E.T., Y.K., T.N., T.S., T.M.
- Data curation: N.J., N.A., M.K., H.S, T.M
- Writing – original draft: N.J., M.K
- Writing – review & editing: All authors
- Supervision: E. K., N. M., and T. B.
  All authors have read and approved the final manuscript.

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# Figures

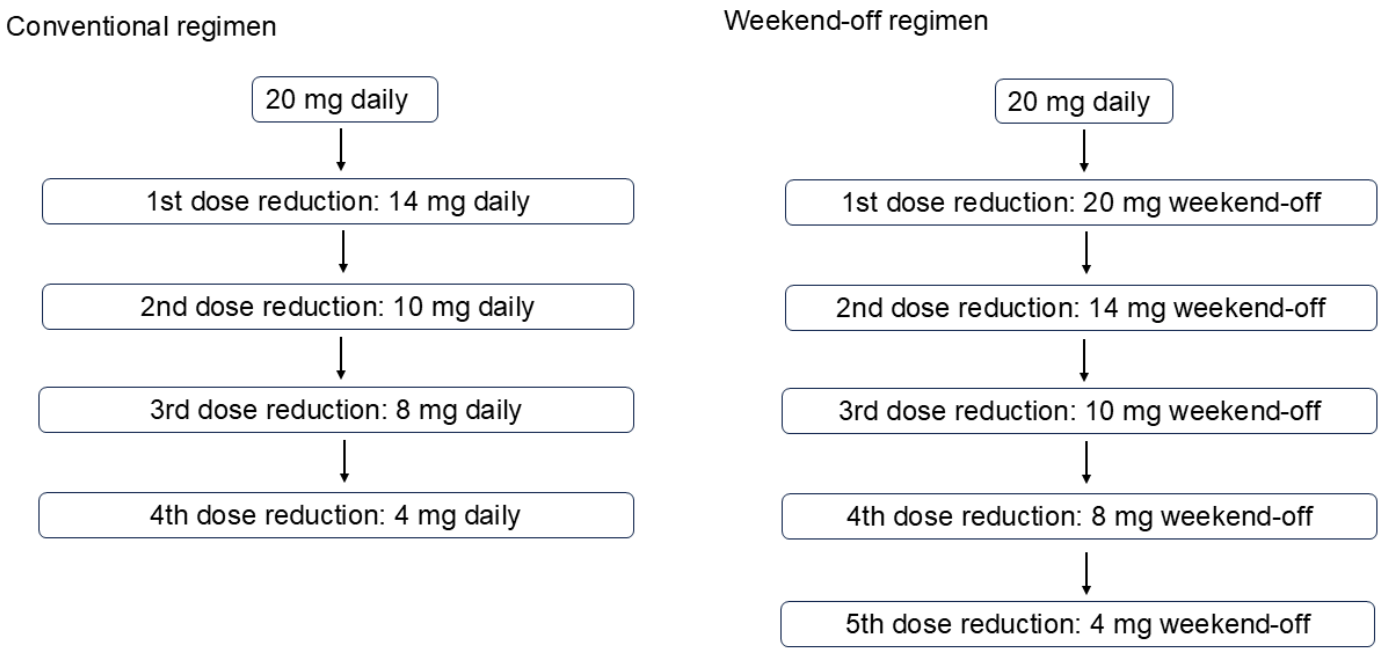



**Fig.1**

## Figure 1

### Treatment protocol

Dose modification strategy for lenvatinib with the weekend-off regimen. After confirming grade ≥3 AEs, proceed to the next dose-modification phase as indicated.

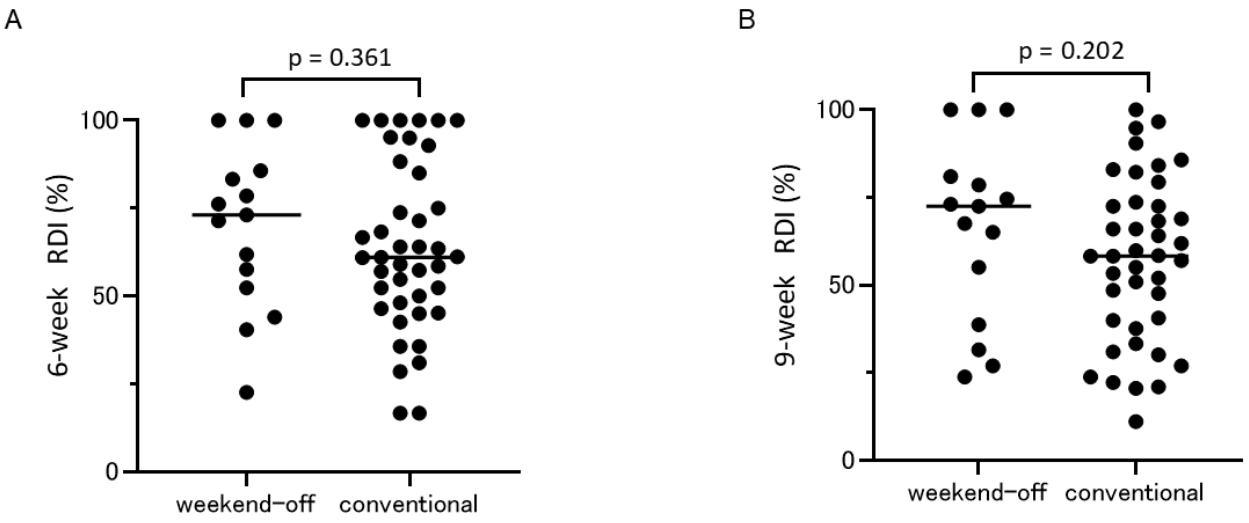



**Fig.2**

## Figure 2

### Comparison of lenvatinib RDI at 6 and 9 weeks between the conventional and weekend-off groups

The relative dose intensity (RDI) of lenvatinib was compared between the conventional and weekend-off groups at weeks 6 and 9. At both time points, the median RDI was higher in the weekend-off group than in the conventional group, although this difference was not statistically significant.

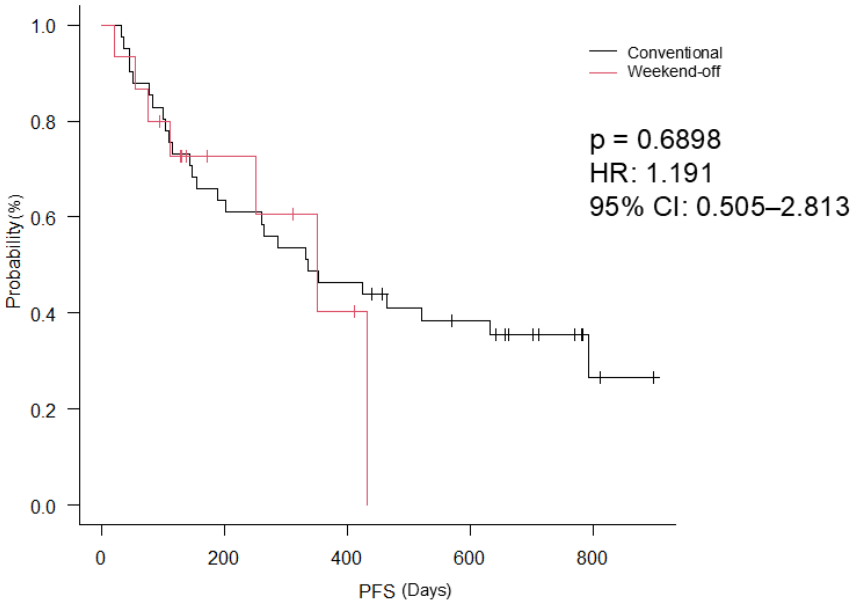



**Fig.3**

## Figure 3

### Kaplan–Meier curves for PFS in the conventional and weekend-off groups

The Kaplan-Meier curve demonstrated an equivalent progression-free survival (PFS) between the conventional and the weekend-off groups. No statistically significant differences were observed (p = 0.6898).

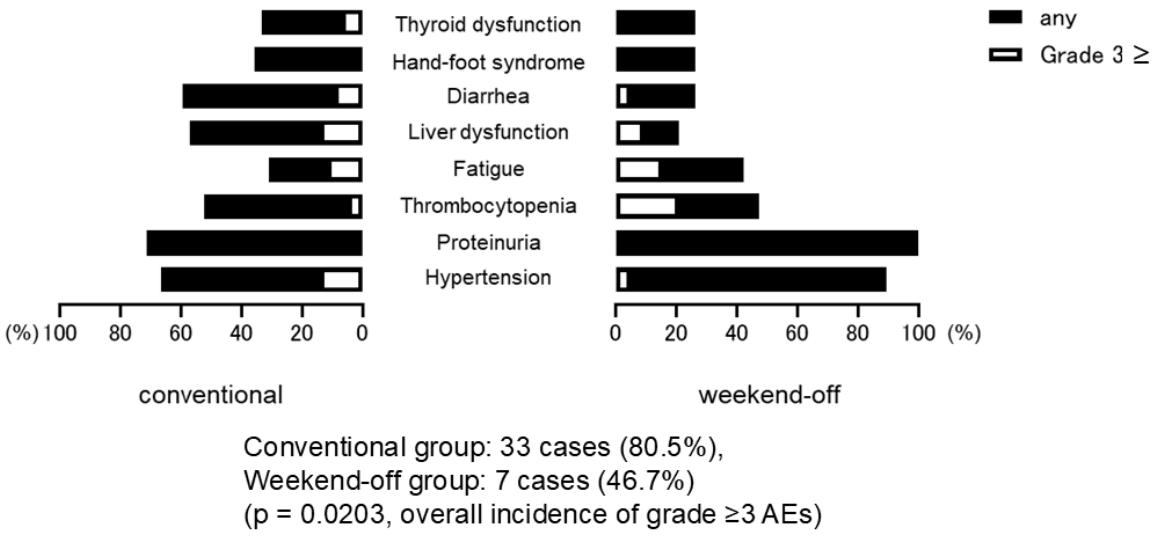



**Fig. 4**

**Figure 4**

**Adverse events**

Incidence of treatment-related adverse events in conventional and weekend-off groups. Bar graphs show the proportion of patients experiencing each adverse event, stratified by severity (grades 1–2 and grade ≥3).

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigSp.pptx