

Administrating Everolimus against neuroendocrine differentiated prostate cancer, a preliminary experience

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Background: Neuroendocrine prostate cancer (NEPC) is a deadly condition, with a median overall survival of less than one year after diagnosis. Although clinical trials are ongoing, an established treatment strategy for NEPC has not yet been developed. A recent clinical trial, RADIANT-4, showed that treatment with everolimus significantly improved survival in patients with progressive neuroendocrine tumors of the lung or gastrointestinal tract. This study evaluated the efficacy of everolimus against neuroendocrine differentiated prostate cancer as an initial investigation.

Methods: Five patients with neuroendocrine differentiated prostate cancer were treated with everolimus (10 mg daily). In our study, we examined the responses and changes over time of circulating neuroendocrine tumor markers, including neuron-specific enolase (NSE) and pro-gastrin-releasing peptide (pro-GRP). We also

evaluated survival outcomes such as castration-resistant prostate cancer (CRPC)-free survival, overall survival (OS), and cancer-specific survival (CSS).

Results: The median follow-up duration was 32 months. A decline in circulating neuroendocrine tumor markers was observed in all cases. The median decline rate of NSE was -0.417 , and that of pro-GRP was -0.647 ($p = 0.841$). The median CRPC-free survival was 10 months (range: 3–NA). Median CSS and OS were both 32 months (range: 8–NA). Grade 3 adverse events (AEs) included hyperglycemia and pneumonitis. Grade 1 AEs included stomatitis (2 cases), paronychia, and pneumonitis.

Conclusions: Everolimus demonstrated reductions in circulating neuroendocrine markers in this exploratory cohort of prostate adenocarcinoma with neuroendocrine differentiation; however, these findings are descriptive and do not establish treatment efficacy.

Key Words: everolimus, neuroendocrine differentiation, prostate cancer, neuroendocrine tumor markers, neuron-specific enolase, pro-gastrin-releasing peptide

Introduction

Prostate cancer is the most frequently diagnosed cancer in men in the United States and ranks as the second leading cause of cancer-related deaths among men.¹ Most patients are diagnosed with prostate

adenocarcinoma, a tumor type that shares morphological features with luminal prostate cells. This form of prostate cancer is driven by androgen receptor signaling and is usually linked to increased levels of prostate-specific antigen (PSA) in the blood.

Neuroendocrine prostate carcinoma (NEPC) is a rare type of tumor, although its occurrence is on the rise.² NEPC is marked by aggressive tumor behavior, including a loss of PSA production, resistance to androgen deprivation therapy (ADT), the emergence of visceral metastases, and a poor prognosis.³ While NEPC can develop initially (*de novo*), it is more

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frequently observed in cases of castration-resistant prostate cancer (CRPC) following ADT.⁴

Compared to adenocarcinoma, NEPC has a worse prognosis, with survival typically ranging from 7 to 10 months. Because the disease is uncommon, the best treatment approach is not well established. Similar to neuroendocrine carcinomas (NECs) in other organs, platinum-based chemotherapy regimens are often used as the first-line treatment for advanced NEPC. Previously reported treatment combinations include etoposide with cisplatin (EP),⁵ cisplatin with docetaxel,⁶ carboplatin with etoposide,^{7,8} cisplatin combined with etoposide and doxorubicin,⁹ estramustine with etoposide and carboplatin or cisplatin,¹⁰ vincristine, doxorubicin, and cyclophosphamide, or etoposide and cisplatin with or without doxorubicin,¹¹ as well as studies involving multiple regimens.¹² Despite promising response rates reported in several phase II trials, progression-free survival (PFS) and overall survival (OS) remain limited.

A recent clinical trial (RADIANT4) showed that treatment with everolimus significantly improved survival in patients with progressive neuroendocrine tumors of the lung and gastrointestinal tract.¹³ This study explored the effectiveness of everolimus in neuroendocrine differentiated prostate cancer as an initial investigation. context of castration-resistant prostate cancer (CRPC) following ADT.

Materials and Methods

Study design

This retrospective study examined cases that began everolimus treatment at Fuji City Hospital between 2016 and 2017. The inclusion criteria for this study were cases with immunohistochemistry positive for at least one of CGA, CD56, and synaptophysin, and positive for at least one of the circulating tumor markers (NSE, pro-GRP). Exclusion criteria were 1) severe infection, 2) use of immunosuppressants, and 3) interstitial pneumonia.

Five patients with neuroendocrine differentiated prostate cancer were administered everolimus (10 mg daily) combined with ADT with or without an antiandrogen agent. All cases had neuroendocrine differentiation confirmed by immunohistochemistry (IHC) in all cases, with at least one histological neuroendocrine marker (chromogranin A, CD56, or synaptophysin) positive on the initial prostate biopsy. Additionally, all cases exhibited elevated levels of at least one circulating tumor marker (NSE or pro-GRP). We evaluated the responses and kinetics

of circulating neuroendocrine tumor markers (NSE and pro-GRP) and PSA. Additionally, we assessed survival outcomes, including CRPC-free survival, overall survival (OS), and cancer-specific survival (CSS). The normal range of NSE is 0 to 16.3 ng/mL, and the normal range of pro-GRP is 0–80.9 pg/mL. Grading of adverse events (AEs) was defined according to the Common Terminology Criteria for Adverse Events (CTCAE).

This study was approved by the Institutional Review Board of Fuji City General Hospital (Approval No. 282). The requirement for informed consent was waived by the Institutional Review Board of Fuji City General Hospital due to the retrospective nature of the study.

Statistical analysis

We conducted the Mann-Whitney U test, *t*-test, and Fisher's exact test to evaluate differences among the groups. Survival rates were estimated using the Kaplan-Meier method. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using EZR ver.1.65 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).¹⁴

Results

Patient demographics

The demographics of five cases treated with everolimus are presented in [Table 1](#). All cases exhibited neuroendocrine differentiation within conventional prostate adenocarcinoma. The median age at the start of treatment was 75 years (range: 60–78). Levels of PSA, NSE, and pro-GRP were measured at the time of prostate cancer diagnosis. The median PSA level was 895.0 ng/mL (range: 156.1–6851.9 ng/mL), the median NSE was 12.1 ng/mL (range: 9.70–32.70 ng/mL), and the median pro-GRP was 147.9 pg/mL (range: 51.6–297.9 pg/mL). NSE levels above the upper limit of normal (ULN) were observed in two of five cases, while pro-GRP levels above the ULN were found in four of five cases. Only one case had both NSE and pro-GRP levels exceeding the ULN. Regarding IHC, all cases were synaptophysin (SYN) positive; one case was CD56 positive, and chromogranin A (CgA) was negative in all cases. Gleason score (GS) 9 was 3 cases, and GS 10 was 2 cases. Four out of five cases had bone metastases, and four out of five had lymph node (LN) metastases. All patients were treated with ADT. Everolimus was administered at the start of treatment in four of the five cases, while in one case, it

TABLE 1. Patients' demographics

Patient	Age	i-PSA	i-NSE	i-pro GRP	CGA	CD56	SYP	GS	T stage	N stage	M stage
Case 1	75	895.0	12.1	139.6	(-)	(-)	(+)	10	NA	1	1b
Case 2	70	162.2	26.0	51.6	(-)	(-)	(+)	9	2a	1	0
Case 3	67	5394.7	10.3	147.9	(-)	(+)	(+)	9	NA	0	1b
Case 4	77	6851.9	32.7	297.9	(-)	(-)	(+)	9	2c	1	1b
Case 5	78	156.1	9.7	252.7	(-)	(-)	(+)	10	NA	1	1b

Note. age: age at treatment start; i-PSA: initial prostate specific antigen (ng/mL); i-NSE: initial neuron specific enolase (ng/mL); i-pro GRP: initial pro-gastrin releasing peptide (pg/mL); CGA: chromogranin A; SYP: synaptophysin.

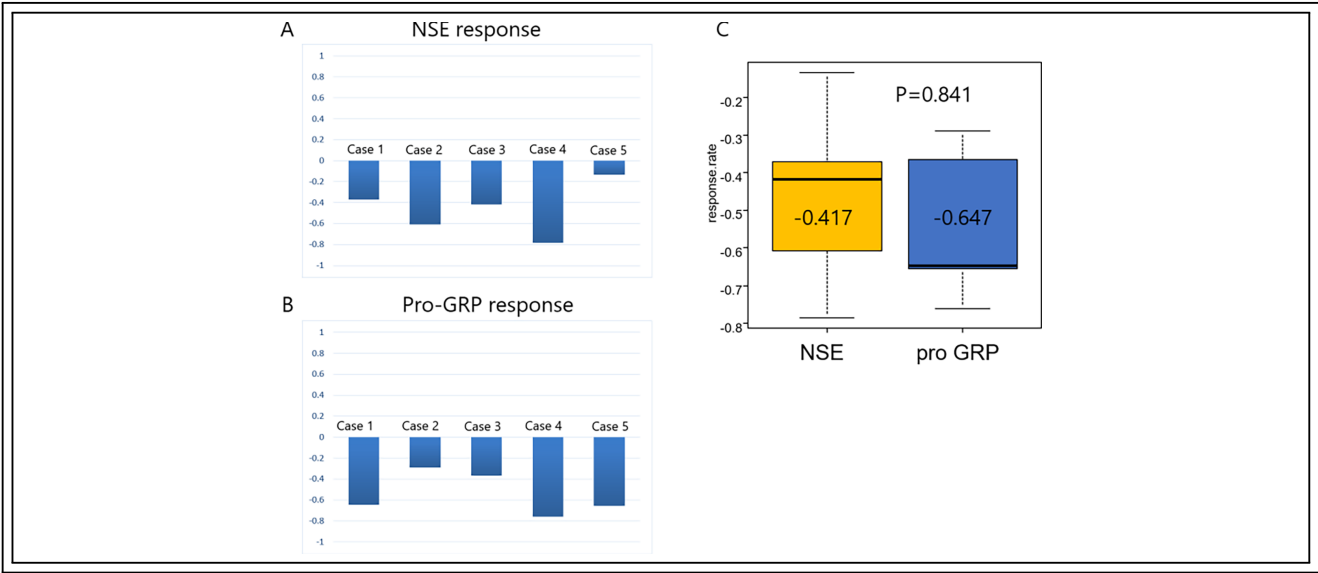


FIGURE 1. Response of circulating neuroendocrine tumor markers: neuron-specific enolase (NSE) and pro-gastrin-releasing peptide (pro-GRP). (A) Waterfall plot of best response of NSE; (B) Waterfall plot of best response of pro-GRP; (C) Comparison of the median response between NSE and pro-GRP

was introduced three months after treatment began. The median follow-up period was 32 months (range: 8–100 months).

Circulating neuroendocrine marker responses

The waterfall plot illustrating the best response in NSE and pro-GRP is shown in Figure 1A,B. Responses were observed in all cases. The median decline rate of NSE was -0.417 , and that of pro-GRP was -0.647 ($p = 0.841$, Figure 1C). The median time to nadir for NSE was 3 months (range: 0–12 months), while for pro-GRP, it was 12 months (range: 0–78 months).

Circulating neuroendocrine marker kinetics

The circulating neuroendocrine marker kinetics of NSE and pro-GRP are shown in Figure 2. The initial

value, nadir value, and the value at the last follow-up for each case are presented.

Survival outcome

CRPC-free survival is shown in Figure 3A. OS from the start of treatment is shown in Figure 3B. And OS from everolimus induction is shown in Figure 3C. Since all causes of death are cancer-specific, OS and CSS are equivalent. The median CRPC-free survival is 10 months (range: 3–NA). Median OS from the start of treatment is 32 months (range: 8–NA). And median OS from everolimus induction is 32 months (range: 5–NA).

Adverse event (AE)

AEs, treatment duration, and reasons for discontinuing everolimus are presented in Table 2. Grade 3 AEs

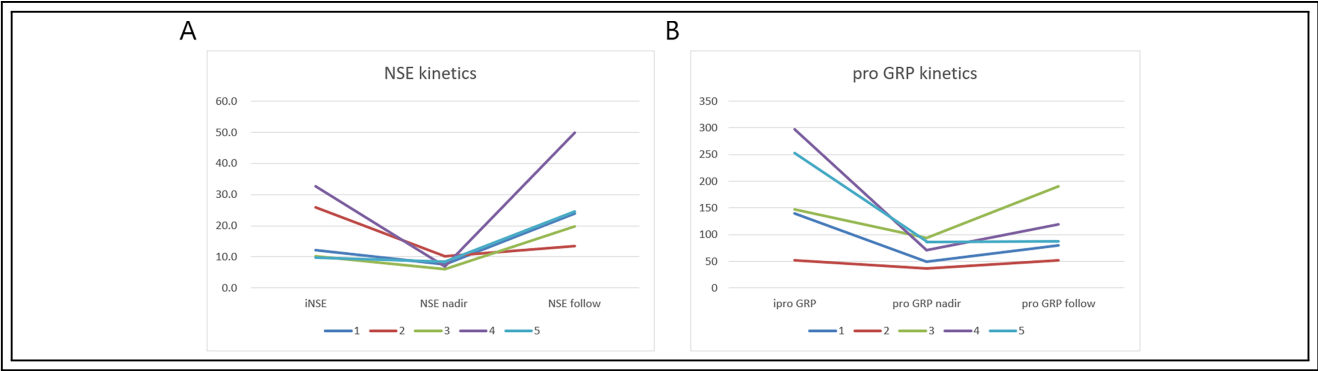


FIGURE 2. Circulating neuroendocrine marker kinetics. (A) Neuron-specific enolase (NSE) kinetics of each case; (B) pro-gastrin-releasing peptide (pro-GRP) kinetics of each case

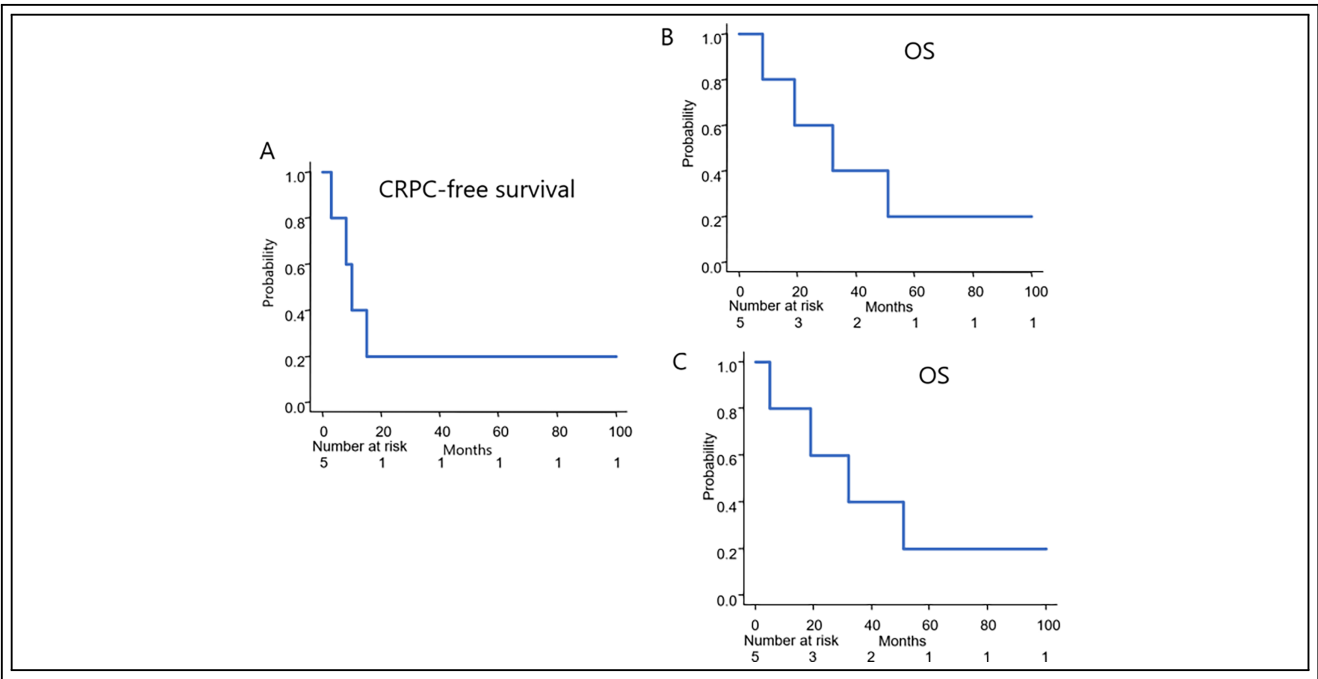


FIGURE 3. Survival outcome. Kaplan-Meier curve of (A) castration-resistant prostate cancer (CRPC)-free survival; (B) overall survival (OS) from the start of treatment; (C) OS following everolimus induction

included hyperglycemia and pneumonitis. Grade 1 AEs included stomatitis (2 cases), paronychia, and pneumonitis. The median duration of everolimus treatment was 2 months (range: 1–7 months). Reasons for discontinuing everolimus included AEs (3 cases), medication-related osteonecrosis of the jaw (MRONJ), and deterioration of the general condition.

Treatment sequences

Treatment sequences are shown in Table 3. Enzalutamide was introduced in 3 cases. Bicalutamide was introduced in 2 cases. Flutamide, abiraterone, and

docetaxel were introduced in 1 case each. External beam radiation therapy (EBRT) was introduced in 1 case.

Discussion

Androgen receptors, which are activated by androgens, are highly expressed in prostate adenocarcinoma. This activation triggers androgen receptor signaling in cancer cells, promoting disease progression. Androgen deprivation therapy (ADT)

TABLE 2. Adverse event and Everolimus duration

Patient	EVE duration	AE	Reason for discontinuing EVE
Case 1	2	Hyperglycemia G3, stomatitis G1, paronychia G1	AE
Case 2	2	Pneumonitis G3	AE
Case 3	1	Pneumonitis G1	AE
Case 4	7	Stomatitis G1	MRONJ (denosumab)
Case 5	5	None	General condition

Note. EVE duration: everolimus duration (months); MRONJ: medication-related osteonecrosis of jaw; AE: adverse event.

TABLE 3. Treatment sequences

Treatment	Number
Bicalutamide	2
Flutamide	1
Enzalutamide	3
Abiraterone	1
Docetaxel	1
EBRT	1

Note. EBRT: external beam radiation therapy.

inhibits androgen receptor signaling, suppresses cancer cell growth, and induces apoptosis.¹⁵ NEPC does not express androgen receptors, is highly aggressive, and is associated with a low survival rate. There are two types of NEPC: *de novo* and treatment-emergent. Treatment-emergent NEPC can result from ADT or radiation therapy.¹⁶ Although *de novo* NEPC is rare, treatment-emergent NEPC has recently been reported to be more common than previously expected. Aggarwal et al. prospectively conducted tumor biopsies of metastatic sites in CRPC patients and analyzed tumor pathology and genomics in those with treatment-emergent small cell prostate cancer (t-SCNC). They concluded that approximately 17% of CRPC patients have t-SCNC, and androgen receptors were expressed in 75% of t-SCNC samples.¹⁷

Although typical NEPC does not express AR as mentioned above, many NEPC cases do express AR, as reported by Aggarwal, suggesting the existence of an intermediate state between adenocarcinoma and neuroendocrine carcinoma. Prostate cancer with neuroendocrine differentiation represents one such intermediate state; however, the clinical characteristics of prostate cancer in this state remain unclear.

Regarding treatment strategies, platinum- and etoposide/irinotecan-based systemic chemotherapies are commonly used to treat NEPC. Several phase II studies have evaluated platinum-based systemic chemotherapy regimens, including carboplatin with docetaxel, carboplatin with etoposide, and cisplatin with doxorubicin and etoposide. The median OS for patients treated with these therapies ranges from 9.6 to 16 months (etoposide with cisplatin (EP),⁵ cisplatin with docetaxel,⁶ carboplatin with etoposide,^{7,8} cisplatin combined with etoposide and doxorubicin,⁹ estramustine with etoposide and carboplatin or cisplatin,¹⁰ vincristine, doxorubicin, and cyclophosphamide, or etoposide and cisplatin with or without doxorubicin,¹¹ as well as studies involving multiple regimens).¹² Recently, Beltran et al. reported a phase II study of the aurora kinase inhibitor alisertib. Alisertib disrupts the interaction between N-myc and its stabilizing factor Aurora-A, thereby inhibiting N-myc signaling and suppressing tumor growth. The median OS in their study was 9.5 months.¹⁸ The mTOR pathway is a central regulator of cellular proliferation, metabolism, protein synthesis, and autophagy, and it plays a significant role in neuroendocrine tumor activity. The mTOR inhibitor everolimus demonstrated efficacy against pancreatic, lung, and gastrointestinal neuroendocrine tumors in the RADIANT trial.¹³

Although PI3K-AKT-mTOR signaling is implicated in prostate cancer progression,^{19,20} there is no direct evidence that mTOR inhibition is effective in prostate adenocarcinoma with neuroendocrine differentiation. Extrapolation from other neuroendocrine tumors, including small-cell lung cancer, provides only an indirect rationale and should be interpreted cautiously.

In this exploratory study, we administered everolimus with ADT to five patients with prostate adenocarcinoma exhibiting neuroendocrine differentiation. All five cases showed declines in circulating neuroendocrine markers (Figures 1, 2).

However, without radiographic or pathological correlation, these biomarker changes cannot be interpreted as evidence of tumor response or biological modulation.

Regarding survival outcomes, median CRPC-free survival was 10 months (range: 3–NA), and median CSS and OS were 32 months (range: 8–NA). These results may reflect the underlying biological characteristics of adenocarcinoma, subsequent systemic therapy (Table 3), and the overall disease burden, rather than the specific effects of everolimus.

There have been no reports on everolimus therapy for NEPC or prostate cancer with neuroendocrine differentiation, making comparisons of treatment outcomes difficult. Furthermore, survival rates for prostate cancer with neuroendocrine differentiation, as opposed to NEPC, have not been documented. Therefore, although the number of cases is small, this report is considered a benchmark for overall survival and cancer-specific survival in prostate cancer with neuroendocrine differentiation.

Although we cannot definitively assess whether everolimus improved survival rates, tumor markers decreased in all cases, suggesting that everolimus was effective as a treatment.

Regarding the kinetics of NSE and pro-GRP, although there was no significant difference ($p = 0.206$), the median time to pro-GRP nadir was longer (12 months) compared with the median time to NSE nadir (3 months). Considering this alongside the fact that the median duration of everolimus treatment was 2 months, it is possible that everolimus has a greater effect on NSE than on pro-GRP. Regarding NSE kinetics, one patient (case 5) who received everolimus three months after the start of treatment showed an NSE nadir before everolimus administration. However, because the initial NSE level was already low (9.7 ng/mL) and the nadir NSE value was 8.4 ng/mL, it was believed that there was little potential for everolimus to further decrease NSE in this case.

Regarding AEs, two out of five cases (40%) experienced grade 3 AEs (hyperglycemia and pneumonitis). AEs were the cause of discontinuing everolimus in three cases (60%). In a phase 2 trial of everolimus treatment for CRPC,²¹ the main grade 3 or higher AEs reported were fatigue (5/35, 14%), mucositis (4/35, 11%), and anemia (3/35, 9%). However, the AEs observed in this study, specifically hyperglycemia and interstitial pneumonia, were considered more significant.

Given the exploratory nature of this study and the absence of validated response endpoints, no conclusions regarding the efficacy of everolimus can

be drawn. Future studies should incorporate radiographic, pathological, and molecular assessments to clarify whether mTOR inhibition has a role in this disease context.

The following are some limitations of this study. It was retrospective, and the sample size was small. The cohort consisted of adenocarcinoma with neuroendocrine differentiation rather than NEPC, limiting generalizability. The dynamics of biomarkers are descriptive and not established indicators of treatment response. Additionally, everolimus was introduced preliminarily for neuroendocrine-differentiated prostate cancer, and the follow-up regimen was not standardized.

Conclusions

In this exploratory case series of prostate adenocarcinoma with neuroendocrine differentiation, everolimus administration was associated with reductions in circulating neuroendocrine markers. However, these findings are descriptive and do not establish clinical efficacy. Because the cohort consisted of adenocarcinoma with neuroendocrine differentiation and lacked radiographic or pathological response assessment, no conclusions can be drawn regarding the therapeutic value of everolimus in this setting. Future studies incorporating standardized imaging, pathological evaluation, and molecular profiling are required to clarify whether mTOR inhibition has a role in prostate cancers exhibiting neuroendocrine features.

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None.

Author Contributions

Conceptualization: Tatsuya Shimomura; Investigation: Tatsuya Shimomura, Masaya Murakami, Kanako Kasai, Yu Imai, Yuzo Inaba; Methodology: Tatsuya Shimomura; Formal analysis: Tatsuya Shimomura; Writing—original draft: Tatsuya Shimomura; Writing—review & editing: Takahiro

Kimura. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

This study was approved by the Institutional Review Board of Fuji City General Hospital (Approval No. 282). The requirement for informed consent was waived by the Institutional Review Board of Fuji City General Hospital due to the retrospective nature of the study.

Conflicts of Interest

Takahiro Kimura is a paid consultant/advisor for Astellas, Bayer, Janssen, and Sanofi.

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