Influence of response to prior docetaxel on sensitivity to cabazitaxel in prostate cancer patients with PTEN alterations

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Abstract
The purpose of this study was to investigate factors predicting the sensitivity to cabazitaxel therapy in metastatic castration-resistant prostate cancer (mCRPC) patients with phosphatase and tensin homolog deleted from chromosome 10 (PTEN) alterations. This single-institution, retrospective study included 12 mCRPC patients with PTEN alterations who had received cabazitaxel therapy. Five patients (41%) responded to cabazitaxel therapy with a prostate-specific antigen (PSA) level decline of ≥30% from baseline, and all of them had responded to prior docetaxel therapy with a PSA decline of ≥30%. None of the patients with a poor response to prior docetaxel therapy responded well to cabazitaxel therapy. Of the seven patients who did not respond to cabazitaxel and whose PSA declined from baseline was <30%, five (71%) were also refractory to prior docetaxel therapy. The PSA responses to docetaxel and cabazitaxel were significantly correlated (p = 0.027). Kaplan–Meier analysis revealed that progression-free survival (PFS) for cabazitaxel was significantly shorter for prior docetaxel nonresponders (3.3 versus 9.1 months, p = 0.028). Multivariate analysis revealed that a poor response to prior docetaxel (PSA decline <30%) (hazard ratio [HR] = 6.382, 95% confidence interval [CI] 1.172–34.750, p = 0.032) and baseline PSA of ≥20 ng/ml (HR = 33.584, 95% CI 2.332–483.671, p = 0.010) were independent prognostic factors for PFS with cabazitaxel therapy. These results demonstrate cross-resistance between docetaxel and cabazitaxel. The response to prior docetaxel therapy can influence the sensitivity to cabazitaxel therapy in mCRPC patients with PTEN alterations.

KEYWORDS
cabazitaxel, castration-resistant prostate cancer, genetic alteration, prostate-specific antigen response, PTEN

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog deleted from chromosome 10.

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1 | INTRODUCTION

Prostate cancer is one of the most prevalent cancers in men and is associated with significant morbidity and mortality. Despite the approval of taxane-based chemotherapy agents such as docetaxel and cabazitaxel and novel androgen receptor inhibitors in the past few decades, metastatic castration-resistant prostate cancer (mCRPC) remains fatal and has poor clinical outcomes. To provide precise and personalized treatment, a better understanding of the molecular characterization of mCRPC patients is becoming necessary.

DNA damage repair deficiency has been studied in different cancer types and has recently received increasing attention with regard to prostate cancer because of the possible effects on treatment selection and outcomes. Some cases of successful gene therapy for prostate cancer have been reported. Although significant progress has been made in elucidating the genetic factors that influence prostate cancer susceptibility, the current status has not yet been translated into relevant stratifications in the clinical field.

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) acts as a phosphatase regulator of the PI3K/AKT pathway. Loss of PTEN function is among the most common molecular alterations in metastatic prostate cancer and activates AKT signaling, leading to cell proliferation and tumor growth, poor prognosis, and dysregulation of androgen receptor activity.

PTEN has been reported to be functionally lost in ~40%–50% of mCRPC cases in Europe and the United States. In contrast, the rate of PTEN loss in the East Asian population is lower than that in the western population, and few studies have examined PTEN loss in East Asian populations. Patients with mCRPC with PTEN loss have been empirically treated with taxane-based chemotherapy, but until now, no standard treatment has been established and the factors affecting sensitivity to taxanes have not been clearly identified.

The purpose of this study was to analyze the factors predicting sensitivity to cabazitaxel therapy, from clinical data and genetic testing in mCRPC patients with PTEN alterations.

2 | MATERIALS AND METHODS

We performed a retrospective observational study of 12 patients with mCRPC with PTEN alterations who were treated with cabazitaxel chemotherapy and who visited Keio University Hospital between 2020 and 2021. Among the 40 patients who underwent genetic testing for health insurance at the urology department of our hospital between 2020 and 2021, 14 (35%) exhibited PTEN alterations. From these patients, 12 who were treated with cabazitaxel after receiving docetaxel were included in this study.

Patients who did not receive a sufficient number of docetaxel therapy cycles were excluded. All patients were cytologically or histologically diagnosed with prostate cancer and had a radiologically or clinically confirmed metastatic disease. They showed disease progression during previous treatment with complete androgen blockade hormone therapy and docetaxel chemotherapy. Cabazitaxel was administered intravenously to the patients at a dose of 20–25 mg/m² on the first day of each cycle, along with oral prednisolone 10 mg per day.

We retrospectively collected clinical and demographic data from electronic medical records. A dose of 75 mg/m² docetaxel was administered every 3 weeks. Treatment delay or dose modification was deemed permissible based on treatment-related adverse events. Biochemical response to prior docetaxel was defined as a ≥30% decline in prostate-specific antigen (PSA) levels from baseline in patients with mCRPC according to the Prostate Cancer Working Group Criteria. The response to cabazitaxel treatment was also assessed. Progression-free survival (PFS) was defined as the time interval from cabazitaxel initiation to an increased PSA level that was ≥25% above the baseline or nadir PSA level or radiological progression, as indicated in the Response Evaluation Criteria in Solid Tumors guidelines. Overall survival (OS) was defined as the time interval from the diagnosis of mCRPC to the last contact or death. Adverse events were categorized according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

After the approval of FoundationOne CDx, we performed next-generation sequencing using specimens obtained from transrectal or transperineal prostate needle biopsy, transurethral resection of the prostate, prostatectomy, or biopsy of metastatic lesions, specifically lymph nodes, bone, or viscera.

Written informed consent was obtained from all patients, and this study was approved by the Ethics Review Board of Keio University Hospital (ethics board approval numbers: 20.160.084 and 20.180.015).

To compare the continuous variables of the two groups, we used chi-squared analysis. Categorical variables were analyzed using the Mann–Whitney U test. PFS and OS curves were constructed using the Kaplan–Meier method and compared using the log-rank test. To identify the risk factors for recurrence, we performed univariate and multivariate analyses using the Cox proportional hazards model. All tests were one- or two-sided, and a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 27.0.

3 | RESULTS

The characteristics of all patients and differences in response to cabazitaxel are summarized in Table 1. The mean patient age was 66 years (range, 46–79 years), and the Eastern Cooperative Oncology Group performance status scores were 0 and 1 in 11 (91%) and 1 (9%) patients, respectively. The mean baseline serum PSA level was 19.6 ng/ml (range between 0.17 and 127). The major sites of metastases were the lymph nodes (83%), bone (75%), and viscera (8%). All gene alterations in the genetic testing are shown in Table 2.

Regarding PTEN alterations, there were homozygous deletions in seven (58%) patients, large deletions (exon 2–3) accompanying biallelic loss in one (8%) patient, frameshift mutation in three (25%) patients, and splice site mutation in one (8%) patient. Regarding genetic
alterations other than PTEN, androgen receptor amplification was identified in four (33%) patients, tumor protein p53 (TP53) pathogenic alterations in seven (58%) patients, transmembrane serine protease2-ETS related gene (TMPRSS2-ERG) fusion in three (25%) patients, and breast cancer (BRCA) 1/2 alterations in three (25%) patients, including germline BRCA2 pathogenic variants. The mean number of prior docetaxel cycles was 7.5 (range, 2–20). Cabazitaxel was administered as a second-line therapy in two patients, third-line therapy in seven patients, fourth-line therapy in two patients, and fifth-line therapy in one patient. Treatment was generally well tolerated, with a mean of 8.4 cycles (range, 3–28).

After treatment with cabazitaxel, 5 (41%) patients were determined to have responded to cabazitaxel therapy with a PSA decline from baseline of ≥30%, and all of them had responded to prior docetaxel therapy with a PSA decline of ≥30%. None of the patients with a poor response to prior docetaxel therapy responded well to cabazitaxel therapy. Of the seven patients that did not respond to cabazitaxel and whose PSA decline from baseline was <30%, five (71%) were also refractory to prior docetaxel therapy (Figure 1). The PSA response to docetaxel and cabazitaxel was significantly correlated (Table 1, p = 0.027). We could not find any other significant statistical differences in the baseline characteristics between the groups with and without a 30% PSA response to cabazitaxel.

The mean OS from the diagnosis of mCRPC was 49.6 months (range, 10.9 and 95.2); two (16%) patients had died by the time of data cutoff. The mean PFS with cabazitaxel therapy in the entire cohort was 3.5 months (95% CI 2.6–4.5; Figure 2A). The mean PFS with cabazitaxel therapy in the groups with and without a 30% PSA response to prior docetaxel was 3.3 and 9.1 months. The PFS with cabazitaxel was significantly shorter in those that did not respond to prior docetaxel treatment (p = 0.028; Figure 2B). In addition, a statistically significant shortening of PFS with PSA decline <30% (3.3 versus 11.9 months, p = 0.003). There was no significant difference in PFS between the types of PTEN alterations (Figure 2c, p = 0.304).

In the univariate analysis, a poor response to prior docetaxel therapy (PSA decline <30%) (p = 0.047) and PSA ≥20ng/ml prior to cabazitaxel therapy (p = 0.014) was significantly associated with shorter PFS with cabazitaxel therapy (Table 3A). There was no significant correlation between age, PS, metastatic sites, type of PTEN

| TABLE 1 Clinical characteristics of all patients and patients stratified by PSA response to cabazitaxel |
|-----------------------------------------------|--|--|--|---|
|                                               | Entire cohort | PSA decrease in response to cabazitaxel ≥30% | PSA decrease in response to cabazitaxel <30% | p-value |
| Number of cases                               | 12 | 5 | 7 | |
| Age (years)                                   | 66 (46–79) | 63.8 (46–78) | 67.8 (54–79) | 0.498 |
| ECOG performance status                       |          |          |          | |
| 0                                             | 11 (91%) | 5 (100%) | 6 (85%) | 0.583 |
| 1                                             | 1 (9%)  | 0 (0%)  | 1 (15%) | |
| PSA at baseline (ng/ml)                       | 19.6 (0.17–127) | 1.37 (0.17–3.64) | 32.6 (1.69–127) | 0.124 |
| Metastatic sites involved                     |          |          |          | |
| Lymph nodes                                   | 10 (83%) | 4 (80%) | 6 (85%) | 0.682 |
| Bone                                          | 9 (75%)  | 3 (60%) | 6 (85%) | 0.364 |
| Visceral metastasis                           | 1 (8%)   | 1 (20%) | 0 (0%)  | 0.417 |
| PTEN alteration                               |          |          |          | |
| Deletion                                      | 8 (67%) | 2 (40%) | 6 (85%) | 0.311 |
| Mutation                                      | 3 (25%) | 2 (40%) | 1 (15%) | |
| Splice site                                   | 1 (8%)  | 1 (20%) | 0 (0%)  | |
| Other genetic alteration                      |          |          |          | |
| AR amplification                              | 4 (33%) | 2 (40%) | 2 (28%) | 0.576 |
| TP53 mutation                                 | 7 (58%) | 2 (40%) | 5 (71%) | 0.311 |
| TMPRSS2-ERG fusion                            | 3 (25%) | 0 (0%)  | 3 (42%) | 0.159 |
| BRCA1/2 alterations                           | 3 (25%) | 2 (40%) | 1 (15%) | 0.364 |
| Total prior docetaxel cycle                   | 7.5 (2–20) | 8.8 (3–20) | 6.5 (2–16) | 0.555 |
| PSA response to prior docetaxel               |          |          |          | |
| ≥30%                                          | 7 (58%) | 5 (100%) | 2 (28%) | 0.027 |
| <30%                                          | 5 (42%) | 0 (0%)  | 5 (72%) | |

Notes: Means and ranges were provided for continuously coded variables.
Abbreviations: AR, androgen receptor; BRCA, breast cancer; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog deleted from chromosome 10; TMPRSS2-ERG, transmembrane serine protease2-ETS related gene; TP53, tumor protein p53.
alterations, type of genetic alterations other than PTEN, or cycles of docetaxel therapy with shorter PFS.

Multivariate analysis revealed that a poor response to docetaxel therapy (PSA decline <30%) (hazard ratio [HR] = 6.382, 95% confidence interval [CI] 1.172–34.759, \( p = 0.032 \)) and PSA ≥20 ng/ml (HR = 33.584, 95% CI 2.332–483.671, \( p = 0.010 \)) was an independent prognostic indicators of PFS with cabazitaxel therapy (Table 3B). We were unable to analyze the relationship with OS because of the limited number of events.

4 | DISCUSSION

Cabazitaxel was the first drug to show a survival benefit in mCRPC patients who were refractory to docetaxel therapy, and it is widely used in Japan with some studies reporting its efficacy and prognostic factors.\(^{21-27}\) In recent years, cancer genomic medicine has received increasing attention worldwide; however, there have been no reports regarding the impact of genomic profiling on cabazitaxel therapy for prostate cancer. We investigated the genomic profile of patients with mCRPC treated at our hospital to determine the factors that influence the efficacy of cabazitaxel.

Among the various types of genetic alterations, we focused on PTEN and found a relationship between sensitivity to prior docetaxel and cabazitaxel.

Loss of PTEN function, which negatively regulates the PI3K/AKT pathway, commonly occurs in aggressive and difficult-to-treat prostate cancer patients, but the standard treatment strategy is not clear.\(^{14,28}\) Therefore, the results of the analysis of oncological outcomes in this study, focusing on genetic alterations and clinical data, are considered informative for this body of literature.

By genetic testing, the effects of the type of PTEN alterations and genetic alterations associated with PTEN, specifically androgen receptor amplification, TP53 mutations, TMPRSS2-ERG fusion, and BRCA1/2 alterations, on PFS in those treated with cabazitaxel were investigated. Although there was no significant difference, patients with both PTEN alterations and TP53 mutations tended to have a

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**TABLE 2** Detailed information on gene alterations

| Case | PTEN alterations | Variant allele frequency | Copy number status | TP53 alterations | BRCA1/2 alterations | TMPRSS2-ERG fusion | AR amplification (CN value) |
|------|------------------|-------------------------|--------------------|------------------|---------------------|---------------------|----------------------------|
| 1    | p.R233fs*10      | 72.2 (%)                | LOH                | p.R249G          | -                   | -                   | -                          |
| 2    | HD               | -                       | HD                 | -                | -                   | +                   | + (15)                     |
| 3    | c.1027-2A>G      | 64.3 (%)                | LOH                | -                | BRCA2              | p.I332fs*3 (somatic) | + (46)                     |
| 4    | HD               | -                       | HD                 | p.R273C          | -                   | +                   | -                          |
| 5    | deletion (exons 2-3) | -                 | HD                 | p.A86fs*55     | BRCA2 deletion (exon1-11) | -               | + (10)                     |
| 6    | HD               | -                       | HD                 | c.920-8.993+22del104 | -     | -                   | + (116)                    |
| 8    | HD               | -                       | HD                 | -                | p.M1411T (germline) | -                   | -                          |
| 9    | HD               | -                       | HD                 | p.V172F          | -                   | -                   | -                          |
| 10   | p.I203fs*18      | 16.4 (%)                | neutral            | -                | -                   | -                   | -                          |
| 11   | p.T319fs*1       | 15.3 (%)                | neutral            | Y220C            | -                   | -                   | -                          |
| 12   | HD               | -                       | HD                 | HD               | -                   | +                   | -                          |
| 13   | HD               | -                       | HD                 | -                | -                   | -                   | -                          |

Abbreviations: AR, androgen receptor; BRCA, breast cancer; CN, copy number; HD, homozygous deletion; LOH, loss of heterozygosity; PTEN, phosphatase and tensin homolog deleted from chromosome 10; TMPRSS2-ERG, transmembrane serine protease2-ETS related gene; TP53, tumor protein p53.
poorer response to cabazitaxel than those without TP53 mutations (Table 3A, \( p = 0.060 \)). TP53 mutations and PTEN loss are frequently detected in mCRPC cases. It has been reported that TP53 status was an important prognostic factor in mCRPC and acted as a biomarker of poor sensitivity to novel hormonal therapies.\(^9,29,30\) Based on these results, we suggest that TP53 may also be a biomarker for sensitivity to cabazitaxel therapy. In any case, the type of PTEN alteration and the presence of other genetic alterations had no statistically significant influence on the PFS for those treated with cabazitaxel in this study. Therefore, we speculate that sensitivity to cabazitaxel cannot be predicted by the type of PTEN alterations or other genetic alterations associated with PTEN loss, although this might be due to the small cohort size at present.

Among mCRPC patients who did not have PTEN alterations according to genetic testing results for health insurance, six were treated with both docetaxel and cabazitaxel. MYC amplification was identified in two patients, SPOP mutation in two, CDK 12 mutation in one, and ASXL 1 mutation in one. Among the cases with MYC amplification and SPOP mutation, one each showed resistance to prior docetaxel therapy but responded to cabazitaxel therapy. These results were in contrast with those for cases with PTEN alterations. One patient with ASXL 1 mutation was resistant to both prior docetaxel therapy and cabazitaxel therapy. One patient with CDK 12 mutation was sensitive to prior docetaxel therapy but not to cabazitaxel therapy. Although we cannot be certain because of the small number of cases, we believe that the results of this study cannot help in predicting the influence of response to prior docetaxel on sensitivity to cabazitaxel in mCRPC patients with genetic alterations other than PTEN.

We previously reported a PFS of 4.4 months in mCRPC patients;\(^26\) however, this study showed a shorter PFS of 3.5 months in the total cohort, suggesting that the effect of cabazitaxel in mCRPC patients with PTEN alterations may be limited. Among them, the PSA response rate and PFS with cabazitaxel were

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**Figure 2** (a) Kaplan-Meier curves for progression-free survival (PFS) for cabazitaxel therapy in the total population (\( n = 12 \)). The mean PFS with cabazitaxel is 3.5 months. (b) Kaplan-Meier curves for PFS with cabazitaxel therapy in the docetaxel response-specified population. The mean PFS with cabazitaxel is 3.3 months in poor response to docetaxel group and 9.1 months in good response to docetaxel group. There was a significant difference (\( p = 0.028 \)). (c) Kaplan-Meier curves for PFS with cabazitaxel therapy in the type of PTEN alterations-specified population. The mean PFS with cabazitaxel is 3.5 months in PTEN deletion patients and 9.1 months in PTEN mutation or splice site patients. There was no significant difference (\( p = 0.304 \)).
significantly worse in those not responding to prior docetaxel therapy with a PSA decline <30%. In other words, patients who had a poor response to prior docetaxel therapy were also cross-resistant to cabazitaxel therapy.

We believe that evaluating the efficacy of docetaxel and cabazitaxel would help patients and physicians to decide whether to introduce cabazitaxel. To the best of our knowledge, this is the first report to demonstrate that a poor response to prior docetaxel therapy is also associated with a poor response to cabazitaxel therapy as a sequential therapy in mCRPC patients with PTEN alterations. These results suggest that in mCRPC patients with PTEN alterations who have been treated with docetaxel, sensitivity to prior docetaxel therapy should be considered when determining the following agents. If sensitivity to docetaxel is poor, therapeutic agents targeting the genetic alterations should be investigated instead of cabazitaxel as sequential therapy, or neuroendocrine tumors are frequently detected in mCRPC patients with PTEN loss; therefore, re-biopsy of the lesions should be considered.

We need to mention that this report has some limitations. This study had a retrospective design and involved a relatively small number of patients; therefore, additional validation should be performed in a prospective multicenter study including patients of different races or ethnicities based on our study. Because this study included cases referred from other hospitals, it was not possible to fully evaluate pathology specimens at the time of initial examination in some cases. Therefore, it was difficult to include a control group with patients for whom PTEN was confirmed to be intact by immunohistochemistry at the time of diagnosis.

In conclusion, our study found that a poor response to prior docetaxel treatment was an independent prognostic indicator of PFS with cabazitaxel therapy. The results suggest that prior docetaxel treatment can influence the sensitivity to cabazitaxel treatment in patients with mCRPC with PTEN alterations.

TABLE 3A Results of univariate analysis influencing progression-free survival with cabazitaxel therapy

| Variables                        | N   | Univariate analysis | p-value |
|----------------------------------|-----|---------------------|---------|
| Age (years)                      |     |                     |         |
| ≥70                              | 7 (58%) | 0.181               |         |
| <70                              | 5 (42%) |                   |         |
| ECOG PS                          |     |                     |         |
| 0                                | 11 (91%) | 0.966               |         |
| 1                                | 1 (9%)           |                    |         |
| PSA (ng/ml)                      |     |                     |         |
| ≥20                              | 3 (25%) | 0.014               |         |
| <20                              | 9 (75%) |                   |         |
| Lymph nodes metastasis           |     |                     |         |
| Yes                              | 10 (83%) | 0.338               |         |
| No                               | 2 (17%)           |                    |         |
| Bone metastasis                  |     |                     |         |
| Yes                              | 9 (75%) | 0.144               |         |
| No                               | 3 (25%) |                   |         |
| PTEN deletion                    |     |                     |         |
| Yes                              | 8 (67%) | 0.309               |         |
| No                               | 4 (33%) |                   |         |
| PTEN mutation / splice site      |     |                     |         |
| Yes                              | 4 (33%) | 0.401               |         |
| No                               | 8 (67%) |                   |         |
| AR amplification                 |     |                     |         |
| Yes                              | 4 (33%) | 0.595               |         |
| No                               | 8 (67%) |                   |         |
| TP53 mutation                    |     |                     |         |
| Yes                              | 7 (58%) | 0.060               |         |
| No                               | 5 (42%) |                   |         |
| TMPRSS2-ERG fusion               |     |                     |         |
| Yes                              | 3 (25%) | 0.194               |         |
| No                               | 9 (75%) |                   |         |
| BRCA1/2 alterations              |     |                     |         |
| Yes                              | 3 (25%) | 0.368               |         |
| No                               | 9 (75%) |                   |         |
| Total prior docetaxel cycle      |     |                     |         |
| ≥10                              | 5 (42%) | 0.514               |         |
| <10                              | 7 (58%) |                   |         |
| PSA response to prior docetaxel  |     |                     |         |
| ≥30%                             | 7 (58%) | 0.047               |         |
| <30%                             | 5 (42%) |                   |         |

Abbreviations: AR, androgen receptor; BRCA, breast cancer; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog deleted from chromosome 10; TMPRSS2-ERG, transmembrane serine protease2-ETS related gene; TP53, tumor protein p53.

TABLE 3B Results of multivariate analysis influencing progression-free survival with cabazitaxel therapy

| Variables                              | N   | Multivariate analysis | HR     | 95% CI     | p-value |
|----------------------------------------|-----|-----------------------|--------|------------|---------|
| PSA (ng/mL)                            |     |                       |        |            |         |
| ≥20                                    | 3 (25%) | 33.584              | 2.332–483.671 | 0.010 |
| <20                                    | 9 (75%) |                   |         |            |         |
| PSA response to prior docetaxel        |     |                       |        |            |         |
| ≥30%                                   | 7 (58%) | 6.382               | 1.172–34.759 | 0.032 |
| <30%                                   | 5 (42%) |                   |         |            |         |

Abbreviations: CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

In conclusion, our study found that a poor response to prior docetaxel treatment was an independent prognostic indicator of PFS with cabazitaxel therapy. The results suggest that prior docetaxel treatment can influence the sensitivity to cabazitaxel treatment in patients with mCRPC with PTEN alterations.

AUTHOR CONTRIBUTIONS
Conceptualization, T.K.; Methodology, T.K. and H.H.; Formal analysis, K.K. and T.K.; Data curation, K.K., T.K., K.N., Y.Y., H.H., T.T. and
K.M.; Writing – original draft preparation, K.K. and T.K.; Writing – review and editing, T.K. and K.N.; Supervision, H.N. and M.O.; Project Administration, T.K. and M.O.

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CONFLICT OF INTEREST
H. Nishihara and M. Oya are editorial board members of Cancer Science. The other authors have no conflicts of interest.

ETHICAL APPROVAL
Approval of the research protocol by an Institutional Reviewer Board. This study was approved by the Ethics Committee of Keio University Hospital (approval number 20160084 and 20180015). Informed Consent: Consent for publication has been obtained from the patient in print; Registry and the Registration No. of the study/trial: N/A; Animal Studies: N/A.

ETHICAL APPROVAL
This study was approved by the Ethics Committee of Keio University Hospital (approval number 20160084 and 20180015). Informed Consent: Consent for publication has been obtained from the patient in print; Registry and the Registration No. of the study/trial: N/A; Animal Studies: N/A.

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