Exploration of Targeted Anti-tumor Therapy

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# First-line discontinuation and subsequent therapy in the era of upfront intensification for metastatic hormone-sensitive prostate cancer: a real-world analysis

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**Academic Editor:** Nicola Normanno, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Italy
**Received:** March 8, 2026 **Accepted:** September 3, 2026 **Published:** November 24, 2026

**Cite this article:** Sato H, Narita T, Sekine Y, Shinohara M, Kawashima Y, Sato H, et al. First-line discontinuation and subsequent therapy in the era of upfront intensification for metastatic hormone-sensitive prostate cancer: a real-world analysis. Explor Target Antitumor Ther. 2026;7:1002415. https://doi.org/10.37349/etat.2026.1002415

## Abstract

**Aim:** Treatment intensification has become standard first-line therapy for metastatic hormone-sensitive prostate cancer (mHSPC). However, real-world discontinuation patterns and their impact on subsequent treatment remain insufficiently characterized. We aimed to evaluate first-line discontinuation and subsequent therapy administration rates in clinical practice.

**Methods:** This retrospective multicenter study analyzed 1,067 patients in the AGEHA real-world database. Patients received either androgen deprivation therapy ± bicalutamide (ADT/CAB) or upfront intensification therapy including androgen receptor pathway inhibitors or docetaxel. The primary endpoint was the first-line discontinuation rate. First-line discontinuation was defined as permanent discontinuation because of progressive disease (PD), adverse events (AEs), death, or other documented reasons. The secondary endpoint was the subsequent therapy administration rate among patients who discontinued first-line treatment.

**Results:** Among 1,056 eligible patients, 643 received upfront intensification therapy and 413 received ADT/CAB as a historical reference cohort. In the upfront intensification cohort, first-line discontinuation occurred in 338 patients (52.6%) and varied markedly across regimens, ranging from 28.1% with ADT plus enzalutamide to 84.7% with ADT plus docetaxel. Subsequent therapy administration after discontinuation also differed across upfront intensification regimens, ranging from 44.1% with ADT plus enzalutamide to 77.3% with ADT plus apalutamide. Heterogeneous transition patterns, including AE-related

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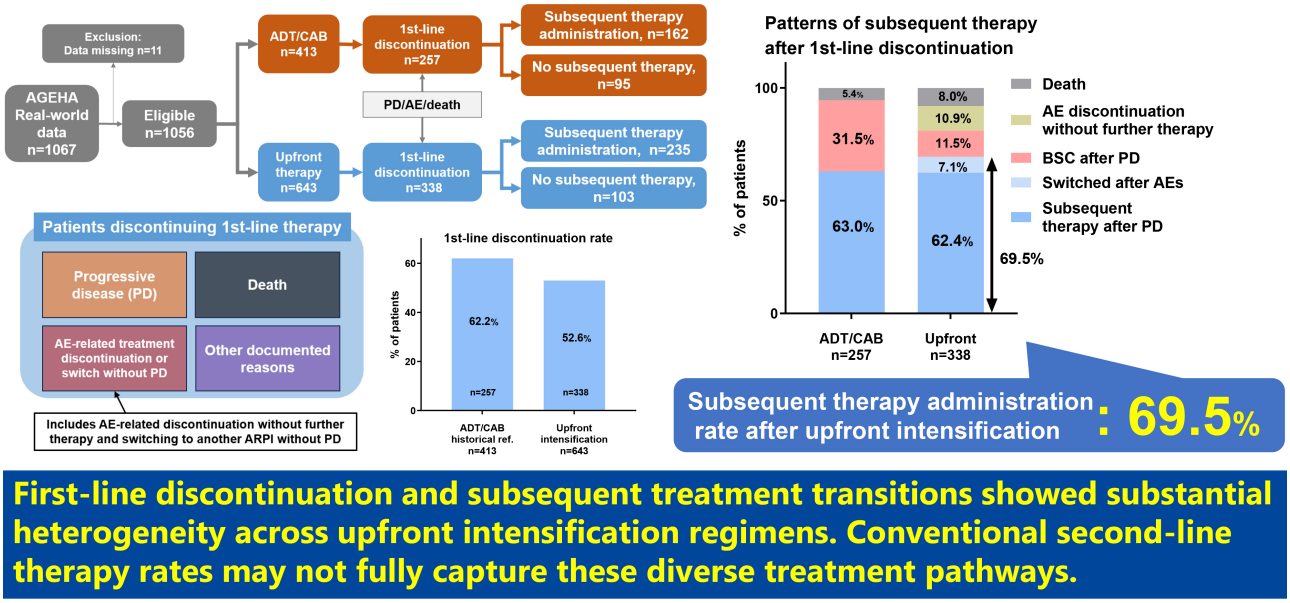
discontinuation, switching without PD, best supportive care (BSC) after PD, and death, were observed. In the historical ADT/CAB reference cohort, first-line discontinuation and subsequent therapy administration rates were 62.2% and 63.0%, respectively.

**Conclusions:** In the upfront intensification era, first-line discontinuation and subsequent treatment transitions showed substantial heterogeneity across regimens. AE-related discontinuation and switching without PD created treatment pathways that are not fully captured by conventional second-line therapy analyses. The ADT/CAB cohort served as a historical reference rather than a contemporary comparator, and differences between cohorts should therefore be interpreted with caution.




**Graphical abstract. Treatment discontinuation and subsequent therapy in metastatic hormone-sensitive prostate cancer (mHSPC).** AE: adverse event; ARPI: androgen receptor pathway inhibitor; ADT: androgen deprivation therapy; CAB: combined androgen blockade; BSC: best supportive care; ref.: reference.

## Keywords

metastatic hormone-sensitive prostate cancer, second-line therapy, subsequent therapy, real-world data, treatment discontinuation

## Introduction

Treatment strategies for metastatic hormone-sensitive prostate cancer (mHSPC) have evolved substantially over the past decade [1–4]. In the hormone-sensitive setting, intensification with androgen receptor pathway inhibitors (ARPIs) or docetaxel (DOC) in addition to androgen deprivation therapy (ADT) has become widely adopted in clinical practice [5–17]. These approaches have improved survival outcomes in clinical trials and are now frequently used as first-line treatment in routine care [18–20].

However, long-term outcomes depend not only on first-line efficacy but also on access to subsequent therapy. First-line therapy may be discontinued because of disease progression, adverse events (AEs), patient preference, or death. Even in randomized controlled trials (RCTs), subsequent therapy is reported; however, its administration is not protocol-mandated and may be influenced by trial-related factors. In clinical practice, treatment sequencing is more heterogeneous and shaped by patient characteristics, tolerability, and physician decision-making [21–29]. Despite the central importance of treatment sequencing, real-world data describing first-line discontinuation and subsequent therapy administration remain limited [30–33].

Moreover, discontinuation and transition patterns may differ across specific first-line regimens. Variations in patient selection, toxicity profiles, and clinical judgment may influence both treatment

durability and subsequent therapeutic access. Understanding these real-world treatment dynamics is essential to clarify how mHSPC strategies function in clinical practice. Therefore, we conducted a multicenter real-world study to describe first-line discontinuation and subsequent treatment transitions in mHSPC and to characterize how these patterns varied across initial treatment strategies in routine clinical practice. This study was intended to describe real-world treatment pathways rather than to estimate the comparative effectiveness of specific treatment strategies.

## Materials and methods

### Study design and ethics statement

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Hirosaki University Graduate School of Medicine (2019-099-3 and 2021-158-2). The ethics committee waived the need for informed consent due to the retrospective nature of the study. An opt-out approach was used to provide patients with the opportunity to refuse participation.

### Study population and patient selection

We analyzed data from the Japanese multicenter AGEHA database, which includes consecutive patients treated in real-world practice at Ageo Central General Hospital, Hirosaki University Hospital, Akita University Hospital, and their affiliated institutions in Japan [34, 35]. Patients who initiated first-line systemic therapy between January 2014 and July 2025 were eligible. Since ARPIs became reimbursed for castration-resistant prostate cancer in 2014 in Japan, we included patients treated from 2014 onward to standardize the intensity of subsequent therapy.

### Treatment classification

First-line therapy was defined as the initial systemic treatment strategy initiated for mHSPC. Treatment strategies were categorized as ADT/combined androgen blockade (CAB) or upfront intensification. Because ADT with or without a first-generation antiandrogen is no longer a guideline-recommended first-line strategy for most patients with mHSPC, the ADT/CAB group was treated as a historical reference cohort rather than a contemporary comparator. The ADT/CAB group included ADT alone or ADT combined with a first-generation antiandrogen, predominantly bicalutamide (CAB). Upfront intensification was defined as ADT combined at treatment initiation with abiraterone acetate (ABI), apalutamide (APA), enzalutamide (ENZ), DOC, or DOC plus darolutamide (DARO). Although these regimens differ in mechanism, efficacy, and toxicity, they were grouped together for the overall descriptive analysis and were also evaluated separately by individual regimen.

### Patients and variables

Demographic and clinical variables collected included age, Eastern Cooperative Oncology Group performance status (ECOG PS), Gleason score, CHAARTED tumor-volume category, extent of disease (EOD), first-line treatment strategy, specific upfront intensification regimen, and reason for first-line discontinuation. First-line discontinuation was defined as permanent discontinuation of the initial treatment strategy because of progressive disease (PD), AEs, death, or other documented reasons. Patients with ongoing treatment, dose reduction or temporary interruption without treatment discontinuation, or missing discontinuation information were not classified as having first-line discontinuation.

### Post-discontinuation classification

Among patients who discontinued first-line therapy, subsequent management was classified as: (1) subsequent systemic therapy initiated after PD; (2) AE-related switching to another ARPI without PD; (3) AE-related discontinuation without further systemic therapy; (4) best supportive care (BSC) after PD; or (5) death (Figure 1A). For calculation of the overall subsequent therapy administration rate, both subsequent systemic therapy after PD and AE-related switching without PD were counted as treatment transitions (Figure 1B). However, these categories were reported separately because AE-related switching represents

a non-progression-driven treatment modification rather than conventional second-line therapy after PD. The use of legacy agents, including bicalutamide, flutamide, or estramustine phosphate, was not counted as subsequent systemic therapy and was classified as BSC.

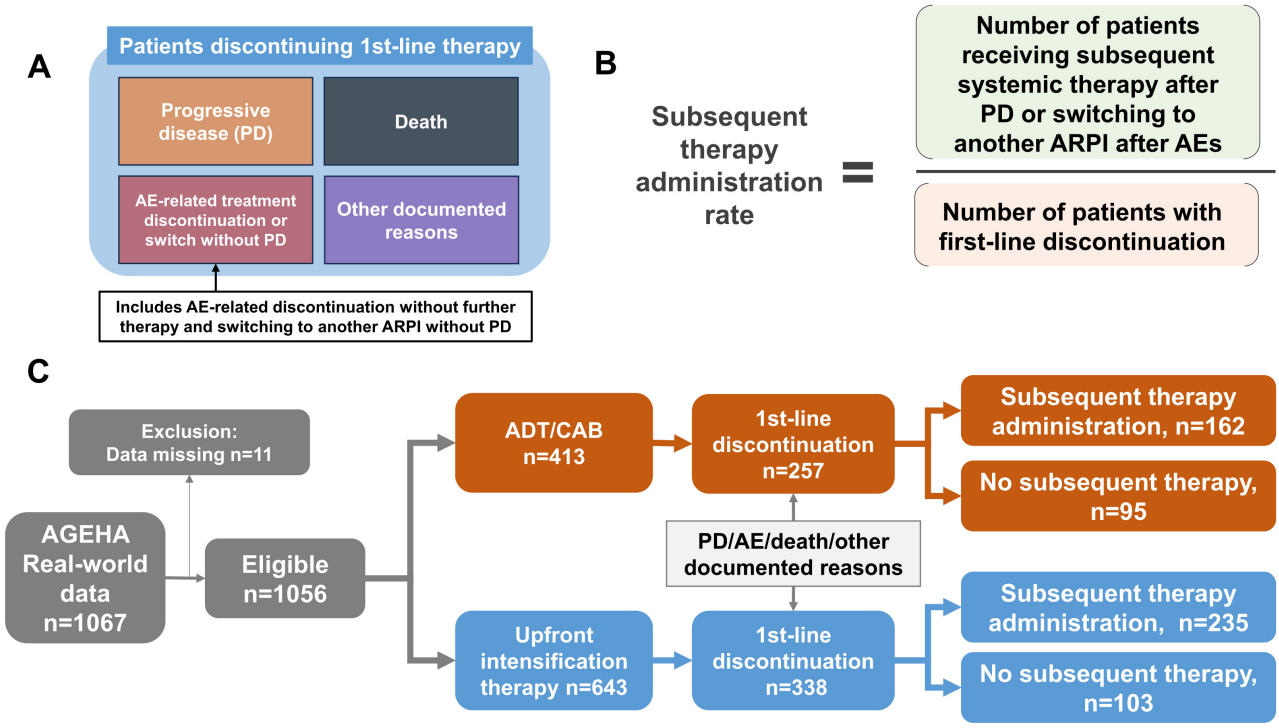



**Figure 1. Study design and definition of subsequent therapy.** (**A**) Conceptual framework of first-line discontinuation. Reasons for first-line discontinuation included progressive disease (PD), AE-related treatment transitions without PD, death, and other documented reasons. AE-related treatment transitions included permanent treatment discontinuation without further systemic therapy, switching to another ARPI without PD, and treatment discontinuation followed by subsequent therapy after later disease progression. (**B**) Definition of the subsequent therapy administration rate. The numerator included patients who received subsequent systemic therapy after PD or switched to another ARPI because of AEs without PD, and the denominator included all patients who discontinued first-line therapy. AE-related switching without PD was included in the overall rate but was reported separately from subsequent systemic therapy after PD. (**C**) Patient flow in the AGEHA real-world cohort. Among 1,067 registered patients, 1,056 were eligible after exclusion of cases with missing data (*n* = 11). First-line treatment consisted of ADT/CAB (*n* = 413) or upfront intensification therapy (*n* = 643). First-line discontinuation occurred in 257 patients in the ADT/CAB group and 338 patients in the upfront group. Among these, 162 and 235 patients, respectively, received subsequent systemic therapy, while 95 and 103 patients did not receive subsequent systemic therapy. AE: adverse event; ARPI: androgen receptor pathway inhibitor; ADT: androgen deprivation therapy; CAB: combined androgen blockade.

## Outcomes

The primary endpoint was first-line discontinuation rate. The key secondary endpoint was receipt of subsequent systemic therapy among patients who discontinued first-line treatment. Failure to receive subsequent therapy was defined as absence of further systemic anticancer treatment after discontinuation. The use of legacy agents such as bicalutamide, flutamide, or estramustine phosphate was classified as BSC.

Subsequent therapy patterns were summarized overall, by treatment strategy (ADT/CAB vs. upfront intensification therapy), and by specific upfront intensification regimens.

As an exploratory analysis, patients in the upfront cohort who discontinued first-line therapy were categorized into five mutually exclusive groups: AE-related discontinuation without further systemic therapy, switching after AEs, subsequent systemic therapy after PD, BSC after PD, and death. Progression-free survival (PFS) and overall survival (OS) were descriptively evaluated across these groups. PFS and OS were calculated from the initiation of first-line therapy to disease progression or death and death from any cause, respectively.

Follow-up duration was calculated from first-line treatment initiation to the last follow-up or death and was summarized according to treatment cohort and upfront intensification regimen. To provide additional temporal context, the interval from first-line treatment initiation to documented PD, death, or last follow-up

was summarized among patients who discontinued upfront intensification. When available, the interval from first-line treatment initiation to documented treatment interruption or discontinuation was also calculated. Because exact treatment interruption or discontinuation dates were not uniformly recorded, formal time-to-discontinuation analyses were not performed.

### Exploratory analysis of AE-related treatment transitions

Among patients receiving ARPI-based upfront intensification, an exploratory logistic regression analysis was performed to identify baseline factors potentially associated with AE-related treatment transitions, defined as AE-related treatment discontinuation or switching to another ARPI without PD. Candidate variables included age, ECOG performance status, CHAARTED tumor volume, diagnostic prostate-specific antigen (PSA), baseline hemoglobin, initial ARPI dose reduction, and ARPI regimen. PSA was log-transformed because of its skewed distribution. Univariable analyses were followed by a parsimonious multivariable model including clinically relevant covariates. Given the limited number of events, these analyses were considered exploratory and were not intended for prediction model development.

As a contextual analysis, published first-line discontinuation and subsequent therapy rates from pivotal phase III trials were summarized descriptively. Because of substantial differences in eligibility criteria, patient characteristics, follow-up procedures, toxicity assessment, treatment duration, and outcome definitions, these trial data were not considered directly comparable with the present real-world cohort. Six pivotal phase III trials with available data on both first-line discontinuation and subsequent therapy were included: LATITUDE (ADT plus ABI vs. ADT) [8], ARCHES (ADT plus ENZ vs. ADT) [6], ENZAMET (ADT plus ENZ with or without DOC vs. ADT plus nonsteroidal antiandrogen with or without DOC) [9], ARASENS (ADT plus DOC plus DARO vs. ADT plus DOC) [12], TITAN (ADT plus APA vs. ADT) [11], and ARANOTE (ADT plus DARO vs. ADT) [13].

### Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Categorical variables were summarized as counts (percentages) and compared using Fisher's exact test. Continuous variables were expressed as medians with interquartile ranges (IQR) and compared between groups with the Mann–Whitney U test. For exploratory survival analyses, PFS and OS were estimated using the Kaplan–Meier method and compared descriptively across groups defined by discontinuation pattern. These analyses were considered exploratory and were not intended to establish causal associations. Statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), GraphPad Prism version 7.00 (GraphPad Software, San Diego, CA, USA), and R software (version 4.2.1). A two-sided $P$ value < 0.05 was considered statistically significant. Because treatment transitions represent time-dependent processes, survival analyses were interpreted descriptively. Given the non-randomized treatment allocation and substantial baseline differences between groups, between-group comparisons were not intended to estimate causal treatment effects and were interpreted as observational associations only. Logistic regression analyses were used to evaluate factors associated with AE-related treatment transitions in the ARPI cohort. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Because of the limited number of events, multivariable analyses were restricted to a parsimonious set of clinically relevant covariates and were interpreted as exploratory.

## Results

### Patient flow and baseline characteristics

Among 1,067 patients registered in the AGEHA database, 1,056 were eligible for analysis after exclusion of patients with missing data (Figure 1C). Of these, 413 received ADT/CAB and 643 received upfront intensification therapy as first-line treatment. Baseline characteristics are summarized in Table 1. Patients treated with ADT/CAB were older than those receiving upfront intensification therapy (median 75 vs. 73 years, $P$ < 0.001). ECOG PS > 1 was more frequent in the ADT/CAB group (15% vs. 7.9%, $P$ = 0.001). Median PSA at diagnosis was lower in the ADT/CAB group (163 vs. 250 ng/mL, $P$ = 0.03). CHAARTED high-

volume disease was more common in the upfront group (75% vs. 66%, $P = 0.002$), and visceral metastasis was also more frequent (22% vs. 16%, $P = 0.03$). Gleason score distribution did not differ significantly when categorized as < 9 versus ≥ 9 ($P = 0.9$). Within the upfront cohort ($n = 643$), regimens included ADT plus ABI (35%), APA (27%), ENZ (19%), DOC (11%), and DOC plus DARO (9%) (Table 1). Baseline characteristics according to specific upfront intensification regimens are shown in Table 2. ENZ-treated patients were older (median 76 years), whereas DOC-containing regimens were used in relatively younger patients. CHAARTED high-volume disease was most frequent in DOC and DOC plus DARO groups (86%), whereas it was less common in the APA group (59%). Visceral metastasis ranged from 13% (APA) to 30% (DOC plus DARO).

**Table 1. Background of patients in the AGEHA database.**

| Variable | ADT/CAB historical reference | Upfront intensification | *P* value |
|---|---|---|---|
| Number of patients, *n* | 413 | 643 | |
| Age, years (median, IQR) | 75 (68, 80) | 73 (68, 77) | < 0.001 |
| ECOG PS, *n* (%) | | | |
| 0–1 | 353 (85.5%) | 592 (92.1%) | 0.001 |
| > 1 | 60 (14.5%) | 51 (7.9%) | |
| PSA at diagnosis, ng/mL (median, IQR) | 163 (32, 816) | 250 (56, 931) | 0.03 |
| Gleason score, *n* (%)[†] | | | 0.9 |
| 6–7, *n* (%) | 62 (15.0%) | 35 (5.4%) | |
| 8 | 76 (18.4%) | 178 (27.7%) | |
| 9 | 197 (47.7%) | 320 (49.8%) | |
| 10 | 61 (14.8%) | 73 (11.4%) | |
| NA | 17 (4.1%) | 37 (5.8%) | |
| CHAARTED high-volume, *n* (%) | 273 (66.1%) | 483 (75.1%) | 0.002 |
| Visceral metastasis (M1c), *n* (%) | 67 (16.2%) | 141 (21.9%) | 0.03 |
| Upfront intensification regimen, *n* (%) | | | |
| ADT + ABI | | 222 (34.5%) | |
| ADT + DOC | | 72 (11.2%) | |
| ADT + APA | | 171 (26.6%) | |
| ADT + ENZ | | 121 (18.8%) | |
| ADT + DOC + DARO (Triplet) | | 57 (8.9%) | |
| Follow-up duration, months, median (IQR) | 27.2 (14.7–42.7) | 27.3 (14.6–48.3) | |

Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using Fisher's exact test. [†]Comparison based on < 9 vs. ≥ 9. ADT: androgen deprivation therapy; CAB: combined androgen blockade; ABI: abiraterone acetate; APA: apalutamide; ENZ: enzalutamide; DOC: docetaxel; DARO: darolutamide; ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: prostate-specific antigen; IQR: interquartile range; NA: not available. The ADT/CAB cohort was treated as a historical reference cohort rather than a contemporary comparator.

Median follow-up was 27.2 months (IQR, 14.7–42.7) in the historical ADT/CAB reference cohort and 27.3 months (IQR, 14.6–48.3) in the upfront intensification cohort (Table 1). Within the upfront intensification cohort, follow-up duration ranged from 12.1 months with ADT plus DOC plus DARO to 56.3 months with ADT plus DOC (Table 2). Among patients who discontinued upfront intensification, the median interval from first-line treatment initiation to documented PD, death, or last follow-up was 18.6 months (IQR, 10.1–36.0). Exact treatment interruption or discontinuation dates were available for 135 of 338 patients; in this subset, the median interval to documented treatment interruption or discontinuation was 5.7 months (IQR, 2.9–17.7).

## First-line discontinuation

First-line discontinuation occurred in 338 of 643 patients receiving upfront intensification therapy (52.6%) and varied markedly across regimens (Figure 2A and B). In the historical ADT/CAB reference cohort, first-line discontinuation occurred in 257 of 413 patients (62.2%). The lowest rate was observed with ADT plus ENZ (34/121, 28.1%), whereas the highest was observed with ADT plus DOC (61/72, 84.7%). Intermediate

**Table 2. Baseline characteristics according to upfront intensification regimen.**

| Variable | ABI | APA | ENZ | DOC | DOC + DARO |
|---|---|---|---|---|---|
| Number of patients, *n* | 222 | 171 | 121 | 72 | 57 |
| Age, years (median, IQR) | 72 (68, 76) | 73 (69, 78) | 76 (72, 81) | 70 (64, 75) | 70 (64, 73) |
| ECOG PS, *n* (%) | | | | | |
| 0–1 | 208 (93.7%) | 159 (93.0%) | 105 (86.8%) | 68 (94.4%) | 52 (91.2%) |
| > 1 | 14 (6.3%) | 12 (7.0%) | 16 (13.2%) | 4 (5.6%) | 5 (8.8%) |
| PSA at diagnosis, ng/mL (median, IQR) | 353 (69, 1093) | 180 (46, 581) | 223 (43, 975) | 313 (117, 1025) | 120 (52, 690) |
| Gleason score, *n* (%) | | | | | |
| 6–7 | 8 (3.6%) | 12 (7.0%) | 10 (8.3%) | 3 (4.2%) | 2 (3.5%) |
| 8 | 75 (33.8%) | 35 (20.5%) | 32 (26.4%) | 19 (26.4%) | 17 (29.8%) |
| 9 | 103 (46.4%) | 83 (48.5%) | 63 (52.1%) | 41 (56.9%) | 30 (52.6%) |
| 10 | 32 (14.4%) | 16 (9.4%) | 10 (8.3%) | 8 (11.1%) | 7 (12.3%) |
| NA | 4 (1.8%) | 25 (14.6%) | 6 (5.0%) | 1 (1.4%) | 1 (1.8%) |
| CHAARTED high volume, *n* (%) | 185 (83.3%) | 100 (58.5%) | 87 (71.9%) | 62 (86.1%) | 49 (86.0%) |
| Extent of bone disease, *n* (%) | | | | | |
| 0 | 17 (7.7%) | 21 (12.3%) | 17 (14.0%) | 4 (5.6%) | 4 (7.0%) |
| 1 | 47 (21.2%) | 63 (36.8%) | 38 (31.4%) | 20 (27.8%) | 14 (24.6%) |
| 2 | 53 (23.9%) | 33 (19.3%) | 30 (24.8%) | 15 (20.8%) | 10 (17.5%) |
| 3 | 81 (36.5%) | 39 (22.8%) | 27 (22.3%) | 28 (38.9%) | 19 (33.3%) |
| 4 | 24 (10.8%) | 15 (8.8%) | 9 (7.4%) | 5 (6.9%) | 10 (17.5%) |
| NA | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Visceral metastasis (M1c), *n* (%) | 54 (24.3%) | 22 (12.9%) | 27 (22.3%) | 21 (29.2%) | 17 (29.8%) |
| Follow-up duration, months, median (IQR) | 33.4 (21.0–60.2) | 25.5 (13.9–41.5) | 22.8 (10.8–30.4) | 56.3 (35.6–83.7) | 12.1 (7.5–18.1) |

ABI: abiraterone acetate; APA: apalutamide; ENZ: enzalutamide; DOC: docetaxel; DARO: darolutamide; ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: prostate-specific antigen; IQR: interquartile range; NA: not available.

rates were observed with ADT plus DOC plus DARO (17/57, 29.8%), ADT plus APA (88/171, 51.5%), and ADT plus ABI (138/222, 62.2%). AE-related discontinuation was most frequent with ADT plus DOC (12/72, 16.7%) and least frequent with ADT plus ENZ (7/121, 5.8%).

## Subsequent therapy administration

Among patients who discontinued first-line therapy in the upfront intensification cohort, subsequent therapy administration was observed in 235 of 338 patients (69.5%) and varied across regimens (Figure 3A and B). In the historical ADT/CAB reference cohort, subsequent therapy administration was observed in 162 of 257 patients (63.0%). Subsequent therapy administration rates were highest after ADT plus APA (68/88, 77.3%) and ADT plus DOC plus DARO (13/17, 76.5%) and lowest after ADT plus ENZ (15/34, 44.1%). Patterns of post-discontinuation management varied across regimens. AE-related discontinuation without further systemic therapy was most frequent after ADT plus ENZ (6/34, 17.6%), whereas AE-related switching without PD occurred most often after ADT plus DOC plus DARO (4/17, 23.5%).

## Exploratory survival analyses according to treatment transition patterns after first-line discontinuation in the upfront cohort

Among 338 patients who discontinued first-line therapy in the upfront cohort, 37 had AE-related discontinuation without further systemic therapy, 24 switched to an alternative ARPI after AEs, 211 received subsequent systemic therapy after PD, 39 received BSC after PD, and 27 died. These groups were defined according to post-baseline treatment transitions and were therefore evaluated descriptively. The median PFS was not reached in the switched-after-AE group and was 97 months in the AE discontinuation group, 15 months in the subsequent therapy group, 13 months in the BSC after PD group, and 19 months in the death group (Figure 4A). The median OS was not reached in the switched-after-AE group and was

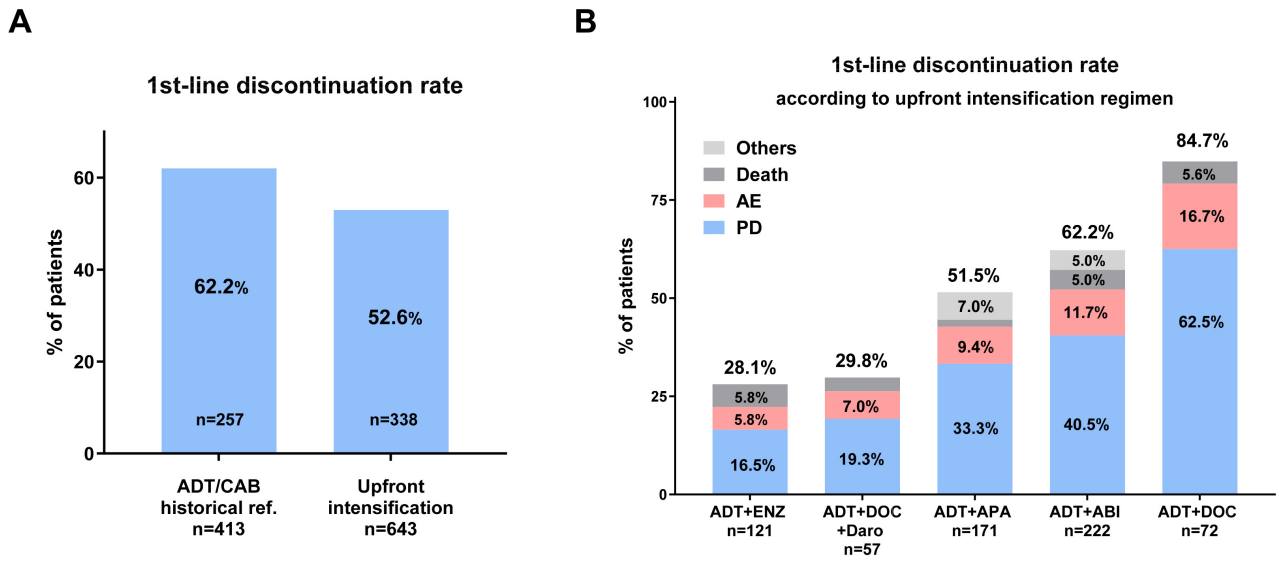



**Figure 2. First-line discontinuation rates.** (**A**) First-line discontinuation rates in the historical ADT/CAB reference cohort and the upfront intensification cohort. The ADT/CAB cohort was retained as a historical reference cohort rather than a contemporary comparator; therefore, no between-cohort statistical comparison is shown. (**B**) First-line discontinuation rates according to specific upfront intensification regimens. The overall discontinuation rate was highest with ADT plus DOC (84.7%) and lowest with ADT plus ENZ (28.1%). AE-related discontinuation was most frequent with ADT plus DOC (16.7%) and least frequent with ADT plus ENZ (5.8%). Component percentages were calculated from the original denominators and rounded independently; therefore, their sum may differ slightly from the displayed total. ADT: androgen deprivation therapy; CAB: combined androgen blockade; AE: adverse event; PD: progressive disease; ENZ: enzalutamide; DOC: docetaxel; Daro: darolutamide; APA: apalutamide; ABI: abiraterone acetate; ref.: reference.

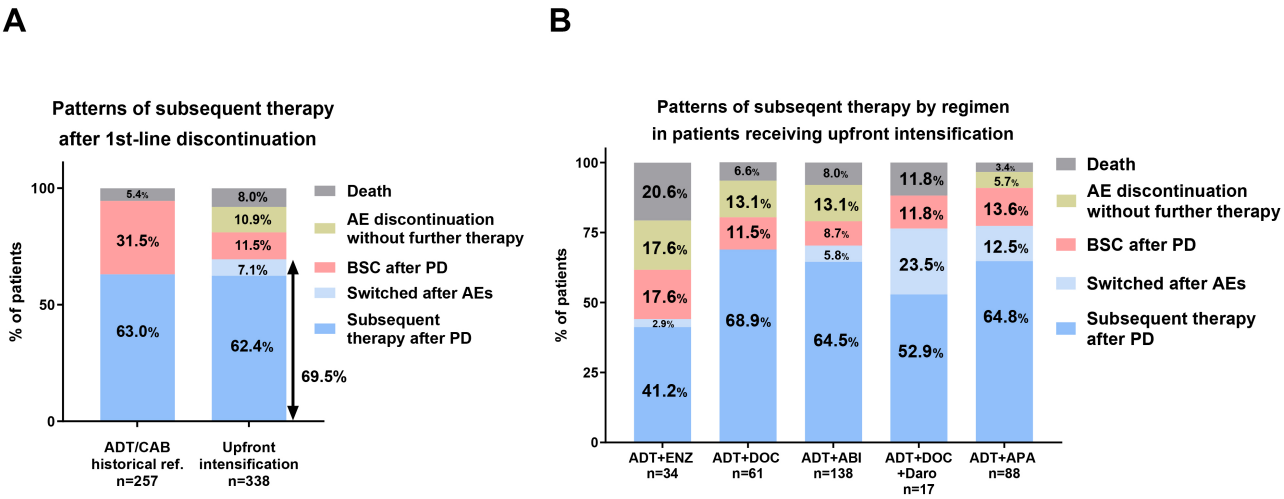



**Figure 3. Patterns of subsequent therapy after first-line discontinuation.** (**A**) Patterns of subsequent therapy after first-line discontinuation according to initial treatment strategy. Among patients who discontinued first-line therapy, subsequent therapy administration was observed in 63.0% of the ADT/CAB cohort and 69.5% of the upfront cohort. (**B**) Patterns of subsequent therapy according to specific upfront intensification regimens among patients who discontinued first-line therapy. Subsequent therapy administration rates were highest with ADT plus APA (77.3%) and ADT plus DOC plus DARO (76.5%) and lowest with ADT plus ENZ (44.1%). AE-related discontinuation without further systemic therapy was most frequent with ADT plus ENZ (17.6%), while switching to another ARPI without PD was most frequent with ADT plus DOC plus DARO (23.5%). ADT: androgen deprivation therapy; CAB: combined androgen blockade; AE: adverse event; BSC: best supportive care; PD: progressive disease; ENZ: enzalutamide; DOC: docetaxel; ABI: abiraterone acetate; Daro: darolutamide; APA: apalutamide.

97 months in the AE discontinuation group, 57 months in the subsequent therapy group, 40 months in the BSC after PD group, and 19 months in the death group (Figure 4B). Because treatment transition categories were defined after treatment initiation and may be affected by selection and immortal time biases, no causal interpretation was intended.

## Exploratory factors associated with AE-related treatment transitions

Among 514 patients receiving ARPI-based upfront intensification, 54 (10.5%) experienced an AE-related treatment transition. No baseline patient characteristic was significantly associated with this outcome in

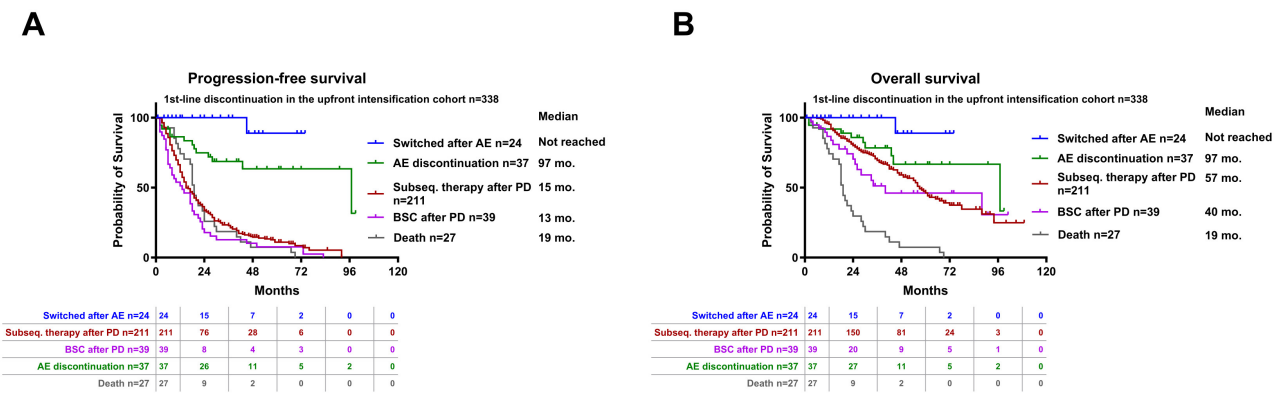



**Figure 4. Exploratory survival analyses according to treatment transition patterns after first-line discontinuation in the upfront cohort.** (**A**) Progression-free survival (PFS) and (**B**) overall survival (OS) among patients who discontinued first-line therapy in the upfront cohort (*n* = 338), stratified into five mutually exclusive groups: switching after AEs (*n* = 24), AE-related discontinuation without further systemic therapy (*n* = 37), subsequent therapy after PD (*n* = 211), BSC after PD (*n* = 39), and death (*n* = 27). Median survival estimates are descriptive because these post-baseline treatment transitions may be affected by selection and immortal time biases. The numbers of events/censored observations for PFS were 1/23, 13/24, 188/23, 39/0, and 27/0, respectively; the corresponding values for OS were 1/23, 10/27, 98/113, 17/22, and 27/0. AE: adverse event; BSC: best supportive care; PD: progressive disease; subseq.: subsequent; mo.: months.

univariable analyses (Table S1). Event rates were 5.8% for ENZ, 10.5% for APA, and 13.1% for ABI. Although ABI was associated with a higher risk than ENZ in the univariable analysis (OR, 2.45; 95% CI, 1.04–5.77; $P = 0.041$), neither ABI nor APA remained significantly associated after multivariable adjustment. These findings should be interpreted cautiously because of the limited number of events and potential confounding by treatment selection.

### Contextual summary of RCT-reported treatment discontinuation and subsequent therapy

Published trial data were summarized solely to provide clinical context and should not be interpreted as direct benchmarks for the present real-world cohort. Using published reports, first-line discontinuation rates and subsequent therapy administration rates in pivotal phase III RCTs were descriptively summarized (Figure S1). Across trials, first-line discontinuation rates varied by study and treatment arm, ranging from 34% to 81%. In the experimental arms, discontinuation rates were 46% in ARANOTE (DARO), 49% in TITAN (APA), 57% in LATITUDE (ABI), 55% in ENZAMET (ENZ), 54% in ARASENS (DOC plus DARO), and 34% in ARCHES (ENZ). In the control arms, the corresponding rates were 72%, 68%, 81%, 80%, 80%, and 68%, respectively. Discontinuation was primarily attributed to PD, whereas AE-related discontinuation ranged from approximately 4.0% to 12% across trial arms (Figure S1A).

Subsequent therapy administration rates, as reported among patients with PD, AE-related discontinuation, or death, ranged from 33% to 66% in the experimental arms and from 43% to 78% in the control arms. Among the experimental arms, the highest rate was reported in ARCHES (ENZ; 66%) and the lowest in ARANOTE (DARO; 33%). Among the control arms, the highest rate was reported in ENZAMET (ADT; 78%) and the lowest in ARANOTE (ADT; 43%) (Figure S1B).

## Discussion

In this large multicenter real-world cohort of patients with mHSPC, first-line discontinuation and subsequent treatment transitions after upfront intensification showed substantial heterogeneity across regimens. Discontinuation occurred through multiple pathways, including PD, AEs, switching without PD, BSC after PD, and death. Subsequent therapy administration after discontinuation also varied across upfront intensification regimens, ranging from 44.1% after ADT plus ENZ to 77.3% after ADT plus APA. These findings suggest that conventional second-line therapy analyses may not fully capture real-world treatment sequencing in the upfront intensification era.

The ADT/CAB cohort was retained as a historical reference cohort because ADT with or without a first-generation antiandrogen no longer represents a contemporary standard first-line strategy for most patients with mHSPC. Therefore, differences between the ADT/CAB and upfront intensification cohorts should not

be interpreted as contemporary comparative estimates. Rather, the historical reference cohort provides context for how treatment discontinuation and subsequent therapy patterns have evolved across treatment eras.

Despite the established survival benefit of upfront intensification, more than half of patients discontinued first-line therapy during follow-up. Discontinuation occurred because of PD, AEs, death, or other documented reasons, reflecting the multifactorial nature of treatment interruption in routine care. The higher observed proportion of first-line discontinuation in the ADT/CAB cohort should not be interpreted as indicating inferior treatment tolerability. The ADT/CAB cohort was older and had poorer performance status, and treatment discontinuation in routine practice may also be influenced by follow-up patterns, adherence, patient preference, physician decision-making, perceived treatment benefit, and access to care. These factors may have contributed to the observed difference between cohorts. Discontinuation rates also varied substantially across upfront intensification regimens, ranging from 28.1% with ADT plus ENZ to 84.7% with ADT plus DOC. This heterogeneity may reflect differences in treatment characteristics, patient selection, duration of exposure, physician decision-making, and tolerability across regimens. Because treatment duration and time to discontinuation were not formally evaluated, crude discontinuation proportions should not be interpreted as direct measures of treatment durability.

Subsequent therapy rates also differed across regimens, with the highest transition rates observed after ADT plus APA (77.3%) and ADT plus DOC plus DARO (76.5%) and the lowest after ADT plus ENZ (44.1%). However, ENZ-treated patients were older and may have had different baseline characteristics, potentially influencing subsequent treatment decisions. These differences likely reflect a combination of patient characteristics, tolerability, and physician decision-making rather than intrinsic differences in therapeutic efficacy alone.

Previous real-world studies have reported patterns of treatment sequencing in mHSPC [30–32, 36]; however, most evaluated subsequent therapy use in the overall cohort rather than specifically among patients who discontinued first-line treatment. By defining the denominator as patients who discontinued first-line treatment, the present study provides a clinically focused estimate of transition to subsequent therapy and may better reflect the practical feasibility of treatment sequencing in routine care.

Exploratory survival analyses further illustrated the complexity of treatment transitions in the upfront intensification era. AE-related discontinuation without further systemic therapy accounted for 10.9% of patients who discontinued upfront intensification therapy, and some patients switched to another ARPI despite the absence of PD. Whether AE-related switching should be classified as "subsequent therapy" remains debatable: from the perspective of first-line discontinuation, it represents a treatment transition, whereas clinically it reflects a non–progression-driven treatment modification. These distinctions complicate conventional second-line analyses and prognostic interpretation. Both the reason for first-line discontinuation and receipt of subsequent therapy represent post-baseline, time-dependent exposures and are therefore susceptible to selection and immortal time biases. In the descriptive analysis, outcomes appeared relatively favorable after AE-related discontinuation or switching, whereas shorter survival was observed among patients managed with BSC after PD or those who died. However, these findings should not be interpreted as evidence of a causal effect of subsequent therapy. Given the limited number of events and the time-dependent structure of these exposures, formal comparative survival analyses were not performed.

In an exploratory analysis of the ARPI cohort, no baseline patient characteristic was clearly associated with AE-related treatment transitions. Although numerical differences were observed across ARPI regimens, these associations were attenuated after adjustment and should be interpreted cautiously because of the limited number of events and potential confounding by treatment selection. Prospective studies incorporating standardized AE assessment, frailty, comorbidities, and regimen-specific monitoring are needed to identify reliable predictors of treatment-limiting toxicity.

The RCT summary was included solely to provide clinical context. Direct comparison with the present real-world cohort is limited by differences in eligibility criteria, follow-up procedures, toxicity assessment,

treatment management, adherence, and documentation; therefore, differences in reported rates should not be interpreted as comparative estimates or evidence of a trial–practice gap. This study was also not designed to identify which patients benefit most from upfront intensification or to determine the optimal subsequent therapy after discontinuation. These questions require comparative effectiveness analyses incorporating treatment-selection factors and time-dependent treatment transitions. Rather, our findings highlight the heterogeneity of treatment pathways that should inform future study design.

This study has several limitations. First, its retrospective, non-randomized design introduced substantial potential for selection bias and confounding by indication. Treatment selection may have been influenced by patient age, performance status, disease burden, comorbidities, physician preference, and patient acceptance, several of which differed between the ADT/CAB and upfront cohorts. Socioeconomic factors and other determinants of treatment choice were not uniformly available. Therefore, between-group comparisons should be interpreted as descriptive associations rather than estimates of causal treatment effects. Second, information regarding loss to follow-up, voluntary treatment discontinuation, non-adherence, financial burden, treatment satisfaction, access to care, clinical trial participation, pharmaceutical educational activities, and patient-support programs was not systematically captured. These unmeasured factors may have influenced both first-line discontinuation and subsequent treatment transitions. Specific AEs leading to discontinuation were also not systematically captured, precluding a reliable comparison of individual toxicities between treatment groups. Third, although median follow-up duration was available and reported by treatment cohort and upfront intensification regimen, exact treatment interruption or discontinuation dates were not uniformly recorded across the entire cohort. Therefore, formal time-to-discontinuation analyses could not be performed. The interval from first-line treatment initiation to documented PD, death, or last follow-up was summarized to provide temporal context, but it should not be interpreted as direct treatment duration. Accordingly, crude discontinuation proportions should be interpreted with caution.

In conclusion, a lower proportion of first-line discontinuation was observed in the upfront cohort than in the ADT/CAB cohort, whereas subsequent therapy use after discontinuation was numerically similar between groups. Heterogeneous discontinuation patterns in the upfront era warrant further investigation.

## Abbreviations

ABI: abiraterone acetate

ADT: androgen deprivation therapy

AE: adverse event

APA: apalutamide

ARPI: androgen receptor pathway inhibitor

BSC: best supportive care

CAB: combined androgen blockade

CI: confidence interval

DARO: darolutamide

DOC: docetaxel

ECOG PS: Eastern Cooperative Oncology Group performance status

ENZ: enzalutamide

EOD: extent of disease

IQR: interquartile range

mHSPC: metastatic hormone-sensitive prostate cancer

OR: odds ratio

OS: overall survival

PD: progressive disease

PFS: progression-free survival

PSA: prostate-specific antigen

RCT: randomized controlled trial

## Supplementary materials

The supplementary figure and table for this article are available at: https://www.explorationpub.com/uploads/Article/file/1002415_sup_1.pdf.

## Declarations


### Acknowledgments

During the preparation of this work, the authors used ChatGPT (OpenAI) and Gemini (Google) solely for English language editing. After utilizing these tools, the authors reviewed and edited the content as necessary and take full responsibility for the final content of the publication.

We thank Ikuya Iwabuchi, Kazuaki Yoshikawa, Hiroyuki Ito, Shoji Nishimura, Satoshi Narita, Hisao Saito, Fumitada Saito, Takaki Ichiyama, Hisashi Sakurai, Anna Yoneyama, Kyo Togashi, Sakae Konishi, Kazutaka Okita, Shogo Hosogoe, Toshikazu Tanaka, Daisuke Noro, Osamu Soma, Yuichiro Suzuki, Noriko Tokui, Kengo Imanishi, Yuki Fujita, and all the participants of the AGEHA Database for their help with data collection.


### Author contributions

SH had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the submitted version.

Conceptualization: SH and Hiroyuki S.

Methodology: SH and Hiroyuki S.

Investigation: All authors.

Data curation: All authors.

Formal analysis: SH.

Writing—original draft: SH and Hiroyuki S.

Writing—review & editing: TN, SH and Hiroyuki S.

Resources: All authors.

Project administration: All authors.

Supervision: CO.

### Conflicts of interest

Shingo Hatakeyama received honoraria from Janssen Pharmaceutical K.K., Astellas Pharma Inc., AstraZeneca K.K., Ono Pharmaceutical Co., Ltd., Bayer AG, Pfizer Inc., Bristol-Myers Squibb, Merck Biopharma Co., Ltd. Shingo Hatakeyama also received research funding support from Ferring Pharmaceuticals Co., Ltd., Kaneka Corporation, Nipro Corporation, and Oyokyo Kidney Research Institute (Public Interest Incorporated Association). Shintaro Narita received honoraria from Janssen Pharmaceutical K.K., Takeda Pharmaceutical Company Ltd., Astellas Pharma Inc., AstraZeneca K.K., Kyorin, Sysmex, and Bayer AG. Tomonori Habuchi received honoraria from Janssen Pharmaceutical K.K., Nippon Kayaku Co., Ltd., Takeda Pharmaceutical Company Ltd., Astellas Pharma Inc., Daiichi Sankyo Company, Ltd., AstraZeneca K.K., Sanofi S.A., Novartis Pharmaceuticals, and Bayer AG. Tomonori Habuchi also received

research funding supports from Mochida Pharmaceutical Co., Novartis Pharmaceuticals Co., Ltd., and Sysmex Co. The other authors have no conflicts of interest to declare.

### Ethical approval

This study was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine (approval numbers: 2019-099-3 and 2021-158-2) and was conducted in accordance with the Declaration of Helsinki.

### Consent to participate

The requirement for informed consent was waived because of the retrospective nature of the study. An opt-out approach was used to provide patients with the opportunity to refuse participation.

### Consent to publication

Not applicable.

### Availability of data and materials

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


### Funding

This work was supported by the Japan Society for the Promotion of Science KAKENHI (grant number [25K02769]). The funder had no role in the study design, data collection, analysis, interpretation, manuscript preparation, or decision to submit the manuscript.



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