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Original Article

Adherence to Oral Treatments in Older Patients with Advanced Prostate Cancer, the ADHERE Study: A Prospective Trial of the Meet-URO Network

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Abstract

Background: Novel androgen receptor signaling inhibitors for prostate cancer (PC) impose the burden of self-administration on older patients overwhelmed by the requirement of many other concomitant medications.

Patients and Methods: This study evaluated the proportion of non-adherence in a 12-month follow-up period and the first 3 months to abiraterone (ABI) or enzalutamide (ENZ). In a prospective multicenter observational cohort study, patients with metastatic castration-resistant PC (mCRPC) aged ≥70 years receiving ABI or ENZ pre- or post-docetaxel were enrolled. Treatment monitoring included pill counting, a self-assessment questionnaire, and clinical diaries at each clinical visit. Non-adherence rates were based on proportions of missed/prescribed pills ratios by pill counting.

Results: Overall, 234 patients were recruited with median age of 78 years (range, 73–82); 86 (37%) were treated with ABI, and 148 (63%) with ENZ. The median follow-up for adherence was seven monthly cycles (IQR: 4–12). The two cohorts were well balanced for baseline characteristics. The percentage of non-adherence by pill counting was slightly higher for ABI than ENZ (5.2% vs. 4.2%, $P < .001$). By self-reporting, patients on ENZ tended to report more frequently than those with ABI forgetfulness as the reason for missing events (42% vs. 17%, $P < .001$). A lower Geriatric G8 score correlated with non-adherence ($P = .004$). Overall survival (OS) was 48.8 months. Patients on ABI had radiographic progression-free survival (rPFS) of 28.4 [24.2–32.5], while for ENZ patients, we reported a median rPFS of 23.1 [18.2–28.1] months.

Conclusion: Physicians tend to treat older mCRPC patients with ENZ. Non-adherence rate is relatively low overall but can be higher with ABI than with ENZ and correlates with the Geriatric G8 score. Forgetfulness is a potential barrier for ENZ.

Key words: adherence; elderly; frailty; prostate cancer; abiraterone; enzalutamide; patient-reported outcome; compliance.

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Implications for Practice

Adherence to the prescription of oral anticancer treatments is underestimated and difficult to measure in oncology, although it may affect treatment efficacy, safety, and costs and is particularly relevant in frail and older people. Our study shows that clinicians prefer enzalutamide to abiraterone when prescribing a new hormonal agent for older patients with castration-resistant metastatic prostate cancer. However, forgetfulness could be an obstacle to adherence to enzalutamide. The non-adherence rate is relatively low but higher with abiraterone than with enzalutamide and is related to patients' frailty as assessed by the Geriatric G8 screening test. Patient and caregiver education alongside appropriate monitoring tools for adherence in clinical practice and trials is topical.

Introduction

In recent years, the advanced prostate cancer (PC) treatment landscape has sensibly changed, with many new hormonal therapies targeting either testosterone production or directly acting on the androgen receptor. These treatments (namely: abiraterone [ABI], enzalutamide [ENZ], apalutamide, and darolutamide) demonstrated their efficacy in different settings from the non-metastatic castration resistance (nmCRPC) status, to the hormone-sensitive (HSPC) and the mCRPC one.[1] The advantage of these drugs is mainly represented by an overall good toxicity profile and oral administration. They offer the convenience of home administration and reduced hospital visits,[2] also representing a preferable option during the COVID-19 pandemic.[3] However, this burdens self-administration, often unsupervised, on a population of older patients overwhelmed by the requirement of many concomitant medications for pre-existing comorbidities.[4-6]

Therefore, it is not surprising that the World Health Organization recognized the lack of adherence, defined as the process by which patients take their medication as prescribed, as an increasingly relevant social and health issue.[7-9]

In clinical trials, treatment adherence is often evaluated as a patient-reported outcome (PRO), a direct report of a patient's condition, not interpreted or modified by the clinician.[10] PROs are considered the gold standard for assessing subjective symptoms and health-related quality of life (QoL). Unfortunately, and especially in older people, PROs tend to underestimate cognitive deterioration, concentration and memory impairment, the adequacy of familiar and social support, all factors that could influence patients' outcomes, management of toxicities, and adherence to oral treatments.

In a previous small case-cohort study, we showed that the overall non-adherence rate, established by drug accountability, was around 5%, mainly due to misperception (77%) and forgetfulness (19%).[11]

Here we report the results of a prospective observational trial involving 6 cancer centers in Italy within the MeetUro national cooperative network.

Materials and Methods

Study Protocol

The Meet-URO-5 Adhere study was a non-profit observational prospective cohort study on older mCRPC patients candidates for ABI or ENZ. It was conducted in 6 centers joining the Meet-Uro—Italian Network for Research in Urologic Oncology. The study was centrally approved by the Catania-1 ethical committee (n.12/2019/CA of the 15 February 2019). The study adhered to the Good Clinical Practice guidelines of the International Conference on Harmonization and the Declaration of Helsinki.

Study Objectives and Endpoints

The primary endpoint was the proportion of non-adherence to the study drugs in a 12-month follow-up period and the first 3 months, according to pill counting and modified and adapted patient-reported Basel Assessment of Adherence Scale (BAAS).[11-13] The non-adherence rate was based on how many pills should be leftover (ie, how many pills would be left on day X of the prescription versus the number of pills still in the bottle on day X)[14]; specifically, as the proportion based on missed/prescribed pills ratio, and, secondarily, as the median of individual proportions over the treatment period. Non-adherence by the adapted BAAS questionnaire was estimated according to the reported missing events, or omission of drug doses and missing reasons; specifically, as the proportions based on the reported missing events/total number of cycles ratio.

Secondary endpoints included: patients' characteristics; evaluation of non-adherence to the fulfilling of the clinical diary; description of self-reported reasons for drug dose missing; evaluation of treatment outcomes, including the PSA decline, the radiographic progression-free survival (rPFS), overall survival (OS); interaction between non-adherence and age, setting of therapy, age-adjusted Charlson comorbidity index (ACCI), Geriatric G8 score, dependency index in the instrumental activities of everyday life (IADL scale), the presence of a caregiver, the number of concomitant drugs, PSA decline, and toxicity.

Patients' Eligibility

Eligible patients had to meet the following criteria for study entry: signed informed consent form; age ≥70 years; histologically documented prostate carcinoma; metastatic or relapsed disease confirmed by imaging, increasing PSA and castrate level of serum testosterone <50 ng/dL, following androgen deprivation therapy; initiation or ongoing treatment with ABI or ENZA in the setting of mCRPC; initiation or ongoing treatment with androgen deprivation therapy; measurable and non-measurable disease; life expectancy ≥12 weeks. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≥4 and prohibitive laboratory values or concurrent medical conditions were exclusion criteria (see protocol in supplementary section).

Adherence to Treatment Monitoring

Screening clinical evaluation included the Geriatric G8 questionnaire,[15,16] ACCI,[17,18] IADL, and a short caregiver evaluation questionnaire consisting of 5 questions regarding the presence, age, degree of kinship, qualification, and working status.

Pill counting, BAAS, toxicity forms, and completion of clinical diaries were reviewed monthly.

Statistical Analysis

Anonymized data were analyzed using SigmaPlot v12.5 (Systat Software Inc). Descriptive statistics were used to characterize the population using frequencies, medians, and quartile values.

Continuous variables were compared by using the Wilcoxon two-sample test. The two-tailed Fisher exact test was used for the statistical comparison of proportions.

The correlation between adherence behavior and potential clinical variables was explored by the Spearman correlation coefficient, using as the cut-off for non-adherence the unsupervised median of individual non-adherence. The Mann–Whitney test was used to compare median values.

Response to treatment by PSA was performed every 2 months and by conventional imaging (either CT scan and/or bone scan) every 4 months. The PSA decline was reported as ≥50% decline from the baseline value (ie, PSA50), and the mean and quartiles of the difference between the PSA baseline and the best response values. The worst degree of toxicity ever suffered by each patient during the treatment was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The rPFS was defined as the time from treatment start to the first objective evidence of radiographic disease progression locally assessed by the clinicians referring to RECIST 1.1 criteria, or death from any cause, whichever occurred first. OS was calculated from the treatment start date until death or the last follow-up. Patients who were not dead or whose disease had not progressed at the time of the final analysis were censored at the date of the last contact. rPFS and OS analyses were estimated by the Kaplan–Meier method and presented with their 95% CIs. Comparisons between survival curves were performed using the Log-Rank test. Patient outcome was analyzed according to the "intention-to-treat" principle.

Receiver operating characteristic (ROC) curves based on significant non-binary factors associated with non-adherence by the Spearman correlation analysis were performed to explore relevant cut-offs.

Adjustment of statistical significance for multiple comparisons was performed by the Bonferroni correction with alpha value = 0.05.

A logistic regression analysis of baseline factors correlated with non-adherence was performed.

Results

Patients' Characteristics

Overall, 234 patients (median age of 78 years [73–82]) undergoing oral treatments for mCPRC were recruited between February 2019 and September 2021. Eighty-six patients were treated with ABI and 148 with ENZ; 69% (162/234) of the patients received the androgen receptor signaling inhibitor (ARSI) in the pre-chemotherapy setting, while 24% (57/234) in the post-chemo and 6% (15/234) had the two ABI or ENZ consecutively [Table 1].

There was no difference between ABI and ENZ patients in terms of Geriatric G8 (14 [12–16] vs. 13 [12–15], P = .08), IADL (6 [5–8] vs. 6 [5–8], P =.63), caregiver support (83% vs. 80%, P = .816), or the number of concomitant medications (3 [1–5] vs. 3 [1–5], P = .671). However, while the median ACCI was 10 in both cohorts, its range was higher for patients on ENZ (10–12 vs. 8–11, P = .028). Otherwise, the two cohorts were well balanced for all the other baseline characteristics, other than the use of steroids (100% vs. 9%, P < .001), since ABI administration requires concomitant corticosteroids supplementation [Table 1]. Approximately half of the study population (57%) experienced grade 1 or 2 toxicities, and only 5% (12/234) had grades 3–4 adverse event, with no difference between the two treatment cohorts [Table 1].

Non-Adherence to ARSIs

Drug accountability was monitored for a median number of 7 cycles (interquartile range [IQR] 4–12) [Table 2].

By pill counting, the non-adherence rate based on the ratio between the total missed/prescribed pills was overall 4.5%, slightly higher for ABI than ENZ (5.2 vs. 4.2, P < .001). The median of individual non-adherence proportions over the treatment period was 2.4%, without significant differences between ABI and ENZ patients (P = .517). ABI treatment was reduced by 50% in 1 patient, while 10 patients in the ENZ cohort had a median dose reduction of 25%.

By self-reporting, 21% of patients reported 6.8% missing events throughout the total number of cycles. Patients on ENZ reported missing events more frequently than ABI (8.8% vs. 3.5%, P = .031). Forgetfulness (37%) and a misperception of the needed drug doses (27%) were the two patient-reported reasons for non-adherence, whilst the number of the pills was not an issue (0%). Forgetfulness was most frequently reported as a reason for missing events by ENZ than ABI patients (42% vs. 17%, P < .001).

About a third of patients (29%) never completed the clinical diary. Among patients who completed the drug accountability diary at least once, 30% were not compliant with diary completion [Table 2].

Data relative to the first 3 months of treatment, confirming similar differences to those observed in the whole observation period, are reported in Supplementary Table S1. Overall, a numerically higher non-adherence rate based on missed pills (5.0%), lower rate of patients (16%) reporting missing events, and not completing the clinical diary (15%) were observed.

Factors Related to Non-Adherence

In the whole period of observation, Geriatric G8 score (P = .004, r = .19), IADL (P = .03, r = 0.1), presence of caregivers (P = .03, r = .19), assumption of concomitant medications (P = .004, r = .13) and G1-2 toxicities (P = .02, r = .16) were correlated to non-adherence according to Spearman rank correlation coefficient [Table 3]. However, after Bonferroni correction, only the Geriatric G8 score remained significantly associated with non-adherence [Table 3].

Considering as cut-off the unsupervised median of individual non-adherence of 2.4%, a Geriatric G8 score of 13 was able to predict non-adherence with a sensitivity of 55% and a specificity of 63% (AUC 0.62, P < .001); while 3 concomitant drugs with a sensitivity of 63% and a specificity of 52% (AUC 0.60, P < .001). An IADL cut-off of 6.5 showed the worst performance, with a sensitivity of 59% and a specificity of 55% (AUC 0.56, P < .086) [Supplementary Fig. S1].

In the logistic regression analysis of baseline factors related to non-adherence, defined by the median of individual non-adherence proportions (ie, with cut-off ≥2.4%), Geriatric G8 score (P < .001), the number of concomitant drugs (P = .004) and the presence of a caregiver (P = .006) were associated with non-adherence, whilst the type of treatment (ie, ABI or ENZ, P = .123) and the IADL (P = .395) did not [Supplementary Table S2].

Table 1. Patient characteristics and clinical outcome.

Characteristic	Abiraterone cohort (n = 86) n (%) or [IQR, 95% CI]	Enzalutamide cohort (n = 148) n (%) or [IQR, 95% CI]	All patients (n = 234) n (%) or [IQR, 95% CI]	P value
Age[a], median, years	78 [73-82]	77.5 [73-82]	78 [73-82]	.50
Gleason score, median	8 [7-9]	8 [7-9]	8 [7-9]	.194
Surgery at diagnosis	38 (44)	50 (34)	88 (38)	.149
Time to CR, mo, median	39.3 [20.5-63.4]	30.1 [11.8-57.1]	31.4 [14.7-58.6]	.072
Sites of metastates[a]				
Lymph nodes (only)	20 (23)	29 (20)	49 (21)	.480
Bone (non-visceral)	56 (65)	107 (72)	163 (70)	
Visceral	10 (12)	12 (8)	22 (9)	
PSA at Tx start, median	11.8 [3.1-29.9]	14.3 [5.4-35.9]	14.0 [4.5-33.9]	.325
Setting of therapy				
Pre-chemotherapy	61 (71)	101 (68)	162 (69)	.222
Post-chemotherapy	17 (20)	40 (27)	57 (24)	
Post-Abi/Enza	8 (9)	7 (5)	15 (6)	
Steroid use[b] (yes)	86 (100)	14 (9)	100 (43)	**<.001**
Charlson score, median	10 [8-11]	10 [10-12]	10 [9-11]	**.028**
Geriatric G8, median	14 [12-16]	13 [12-15]	14 [12-15]	.081
IADL, median	6 [5-8]	6 [5-8]	6 [5-8]	.639
Concomitant therapies, no.	3 [1-5]	3 [1-5]	3 [1-5]	.671
Caregiver (yes)	71 (83)	119 (80)	190 (81)	.816
Toxicity				
G1/G2	43 (50)	91 (61)	134 (57)	.115
G3/G4	1 (1)	11 (7)	12 (5)	.074

Bold indicates statistically significant values.
[a]At the time of initiation of treatment.
[b]During the whole treatment.
Abbreviations: Abi, abiraterone; CI, confidence intervals; Δ, difference between the PSA basal value and the best response value; Enza, enzalutamide; mo., months; G, grade; IQR, interquartile range; Tx, treatment; yr, year.

Clinical Outcomes

One-hundred-sixty-four (72%) had a 50% reduction in PSA, with a median differential PSA decline from the treatment start of 85%. OS was 48.8 months for the whole cohort. Patients on ABI had a median rPFS of 28.4 months [24.2–32.5], while for ENZ patients, we observed a median rPFS of 23.1 [18.2–28.1] months [Table 4].

Using the cut-off of 2.4%, non-adherence was not associated with OS or rPFS in our study population (respectively for values <2.4% vs. ≥2.4%, OS was 54.6 vs. 42.6 months, P = .926; rPFS was 26 vs. 24.8 months, P = .572) [Supplementary Fig. S2].

Discussion

Advanced PC generally affects males older than 65 years old.[19] Overall, the percentage of all cancers diagnosed in older adults will increase from 61% to 70% in the next 10 years; this emphasizes the importance of personalized assessments and strategies for older and possibly frailer cancer patients.[20] Moreover, the increasing availability of oral anticancer treatment in advanced PC has over-imposed on an elderly population of patients the burden of self-administration and drug accountability. Therefore, adherence to oral therapies is becoming an issue for health organizations and physicians, especially when the COVID-19 pandemic has drastically reduced hospital footfall and telemedicine has become a new reality.[21]

Treatment adherence is commonly affected by several factors, which might often be inter-dependent: patient-related (ie, age, personal beliefs, and mental health); disease-related (ie, comorbidities, disease aggressiveness, and polypharmacy); treatment-related (ie adverse effects, toxicities, and treatment duration); social issues (ie, cost of medicines, social support, and presence of a caregiver); and physician-related (ie, doctor–patient relationship, use of guidelines, and patients' education).[4,21]

Therefore, it is paramount to choose the right population of patients to treat with oral anticancer drugs to derive a possible benefit in terms of oncological outcomes and social-economic burden.

The Geriatric G8 is a screening tool containing 8 questions investigating patients' nutritional, mobility, and neuropsychological conditions through questions about food intake, weight loss, mobility, neuropsychological problem, body mass index, prescription drug, and self-perception of health. The total G8 score ranges between 0 and 17, with a score equal to or lower than 14 indicating the need for a complete geriatric evaluation.[22] Low G8 scores have been associated with poor outcomes in prostate cancer patients with localized or advanced disease.[23] Similarly, ACCI has been proposed as a tool for prognostication of survival in PC patients undergoing radical treatments or anticancer drugs for advanced disease.[24-26]

Table 2. Adherence to abiraterone or enzalutamide in the whole period of observation.

Parameter	Abiraterone cohort (*n* = 86)	Enzalutamide cohort (*n* = 148)	All patients (*n* = 234)	*P* value
Assessed cycles				
n (%)	669 (38)	1070 (62)	1739	
Median, *n* [IQR]	8 [4-12]	7 [4-12]	7 [4-12]	.239
Pill counting				
Non-adherence[a], pills *n* (%)	1.941/37.184 (5.2)	4.939/117.096 (4.2)	6.880/154.280 (4.5)	**<.001**
Non-adherence[b], median % [IQR]	3.1 [10.2/0.0]	2.2 [5.4/0.9]	2.4 [7.3/0.7]	.517
Compliance, dose reduction, pts, *n* (%)	1 (1)	10 (7)	11 (5)	.0513
Dose reduction, median % [IQR]	50 [NA]	25 [25-50]	30 [25-50]	
BAAS (patient's reporting)				
Patients missing, *n* (%)	12 (14)	38 (26)	50 (21)	.052
Missing events[c], *n* (%)	23 (3.5)	90 (8.8)	113 (6.8)	**.031**
Missing reasons, *n* (%)				
Forgot	4 (17)	38 (42)	42 (37)	**<.001**
Do not need it	8 (35)	22 (24)	30 (27)	
Quantity	0 (0)	0 (0)	0 (0)	
Other	11 (48)	30 (33)	41 (36)	
Clinical diary				
Non-adherence[d], patients *n* (%)	20 (35)	33 (31)	53 (29)	.6072
Non-compliance[e], patients *n* (%)	29 (34)	42 (28)	71 (30)	.3914

Bold indicates statistically significant values.
[a]Based on the proportion of missed/prescribed pills ratio.
[b]Proportions based on missed/prescribed pills ratio, reported as the median (and IQR) of individual proportions over the treatment period.
[c]Proportions based on reported missing events/total number of cycles ratio.
[d]Proportions based on fulfilled/delivered diary ratio in patients completing at least one diary.
[e]Patients not completing any of the diaries delivered.
Abbreviations: IQR, interquartile range; m, months; *n*, number; NA, not assessable.

Table 3. Factors related to adherence to abiraterone or enzalutamide in the whole period of observation

Variable	Non-adherence[a] *P* value[b] (*rho*)	Effect[c] on adherence
Age, older	.143 (–0.0961)	Worsening
Treatment, Abi vs. Enza	.517 (–0.0426)	Worsening
Setting of therapy, pre-CT vs. post-CT	.612 (0.0333)	Improving
Charlson comorbidity score, higher	.199 (–0.0841)	Worsening
Geriatric G8 score, higher	**.00433 (0.186)**	**Improving**
IADL, higher	**.0324 (0.140)**	**Worsening**
Caregiver presence, yes vs. no	**.0285 (0.195)**	**Worsening**
Concomitant drugs, higher no.	**.0445 (0.131)**	**Worsening**
Δ PSA, higher reduction	.904 (0.00799)	Improving
G1-2 Toxicity, yes vs. no	**.0172 (–0.156)**	**Worsening**
G3-4 Toxicity, yes vs. no	.262 (–0.0736)	Worsening

Bold indicates statistically significant factors.
[a]Based on the individual proportion of missed/prescribed pills ratio.
[b]According to Spearman rank correlation coefficient.
[c]Aiming to interpret the rho correlation coefficient by taking into account the negative value of non-adherence individual proportions and the different direction of variables: for instance, higher Charlson and IADL scores are pejorative, whilst higher Geriatric G8 score and Δ PSA reduction are ameliorative.
Abbreviations: Abi, abiraterone; CT, chemotherapy; Enz, enzalutamide; mo., months; No., number.

In our study, physicians tended to treat older patients with a higher ACCI with ENZ, probably considering the concomitant use of prednisone for ABI, and the potential associated cardiovascular disorders.[27] Nevertheless, ENZ seems to be associated with increased risks of amnesia, cognitive disorders, memory impairment, confused states, and fatigue.[28] It is not surprising that a higher percentage of ENZ patients than ABI patients did not adhere to treatment due to forgetfulness. As not everyone started the observational period for adherence at the start of the anticancer therapy, our results might have 2 possible implications: either ENZ affects memory loss, thus patients are less adherent to treatment, or baseline patients' frailer conditions reflect on mental health and then onto the treatment adherence. Moreover, the other common cause of non-adherence is a misperception of the drug, with patients thinking they do not need to take their dose.

Our data suggest that an easy-to-use and quick screening tool such as the G8 can also be valuable for non-adherence to ABI or ENZ. At the same time, patient diaries are often not completed, thus questioning their use as guides for patients to take the effective drug doses prescribed by the clinician.

Other relevant factors that undermine adherence to oral treatments are the absence of a caregiver, drug-related toxicities, and concomitant drugs, as we previously showed.[11] According to the current analysis, several concomitant medications equal to or higher than three seem to predict the lack of adherence. This represents a key factor, easy to check, that is too often ignored.

Table 4. Treatment efficacy outcomes.

Characteristic	Abiraterone cohort (n = 86) n (%) or [IQR, 95% CI]	Enzalutamide cohort (n = 148) n (%) or [IQR, 95% CI]	All patients (n = 234) n (%) or [IQR, 95% CI]
PSA50	58 (69)	106 (73)	164 (72)
NA	2 (2)	3 (2)	5 (2)
PSA Δ median	(–83) [–97/-30]	(–85) [–98/-42]	(–85) [–98/–39]
Median FU, mo.	17.5 [11.9-23.1]	14.6 [12.1-17.1]	15.4 [12.1-18.7]
PFS, median, mo.	28.4 [24.2-32.5]	23.1 [18.2-28.1)	26.0 [22.8-29.3]
OS, median, mo.	48.8 [34.3-63.3]	42.3 [39.1-45.4]	48.8 [36.8-60.8]

Abbreviations: CI, confidence intervals; Δ, difference between the PSA baseline and best response values; FU, follow-up; mo., months; NA, not assessable; OS, overall survival; PSA50, decline in the PSA ≥50%; rPFS, radiographic progression-free survival.

The non-adherence rate we found in the overall cohort of patients can be considered relatively low and the one-percent difference between the two drug cohorts, albeit statistically significant, is not clinically relevant. Notably, non-adherence in our study was defined as the ratio between missed and prescribed pills, and even a small delta for a ratio could translate into a relevant difference in absolute terms. Indeed, if we considered the total missed pills, they were 6.880 over 154.280 in the overall population. Whether that could be a minor problem in terms of patients' outcomes, as per our study findings of no substantial impact on both rPFS and OS, this still deserves attention for other related issues like, the pharmaco-economical ones. Furthermore, the relatively low non-adherence rate observed should be put in the context of the study observation time length and castrate-resistant disease setting. The non-adherence rate to both the study drugs did not differ between the time point of 3 and 7 months, indicating that even a shorter observational period might well reflect the absolute adherence to treatments. However, we cannot rule out that the non-adherence rate could increase with longer follow-up or when a more prolonged time on treatment is expected, as for the hormone-sensitive disease phase.

ABI seemed to confer on patients a longer rPFS compared to ENZ. However, our study was not designed and powered to show a difference in rPFS. The rPFS evaluation was one of the secondary study endpoints. Intriguingly, in the absence of formal head-to-head studies, this information could be hypothesis-generating, as it is based on a sample size bigger than 200 patients quite well balanced for their baseline characteristics. Nevertheless, it needs confirmation in prospective ad-hoc trials. Moreover, differences in outcomes might be biased by the time of observation for non-adherence within the study, which did not always match with the whole treatment duration.

The main limitation of this study relies on patients' awareness to be monitored, which may have driven them to stick more with the regimen of prescribed medication. The low rates of non-adherence we observed in our study might underrepresent a more significant issue in daily clinical practice. Patients who were enrolled were indeed aware of being monitored and could have been potentially more careful in assuming anticancer treatments. Despite this, we noted a scarce use of clinical diaries. We adopted the ratio between the total missed and prescribed pills by pill counting in the whole population and in the single drug cohorts as the primary measure of non-adherence, while the median of individual non-adherence proportions as the secondary one. This primary measure could not appropriately take into account the inter- and intra-patient non-adherence differences, although focusing on the missed pill numbers would provide a more reliable and pragmatic estimate than the median of individual proportions. This is a topical issue as neither a standard endpoint nor a benchmark is currently available to measure adherence to oral anticancer treatments. Notably, we reported a low rate of severe toxicity with both the study drugs as compared to other trials with those agents. The lower rate of severe toxicity reported in this real-world study might be likely explained by the long-standing experience of clinicians with the two study drugs, including the use of dose reduction to prevent their occurrence, but also the relatively short observation time requested by the study for the monitoring of adherence. Furthermore, we could not properly and prospectively assess the neurocognitive function, as well as the survival outcomes of our patients.

Overall, our analysis is one of the few prospective studies evaluating adherence to oral anticancer drugs, demonstrating that vulnerable patients are more prone to non-adherence but could be easily identified by the G8 questionnaire. Non-adherence is often under-reported by patients, and is primarily due to misperception and forgetfulness in ENZ patients. More importantly, we demonstrated that an appropriate adherence questionnaire should be redesigned as with the adapted BAAS, many patients reported "other" as the reason for missing doses.

In conclusion, a multidisciplinary approach, including identifying patients at risk and interventions involving family caregivers, is encouraged to increase patient awareness and empowerment.

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Conflict of Interest

Pasquale Rescigno: MSD, AstraZeneca (C/A); **Sara Elena Rebuzzi:** Amgen, GSK, BMS, MSD (H, travel expenses); **Ugo De Giorgi:** Pfizer, BMS, MSD, PharmaMar, Astellas, Bayer, Ipsen, Roche, Novartis, Clovis, GSK, AstraZeneca (H), AstraZeneca, Sanofi, Roche (RF); **Orazio Caffo:** AAA, AstraZeneca, Astellas, Bayer, Janssen, Ipsen, MSD, Pfizer Speaker: Ipsen, MSD, AstraZeneca, Astellas, Janssen (C/A); **Davide Bimbatti:** Ipsen, Astellas, Janssen, Novartis, BMS, MSD (C/A, personal fees outside the submitted work); **Vincenza Conteduca:** Janssen, Astellas, Merck, AstraZeneca, Bayer (C/A), Astellas, Janssen, Ipsen, Bayer (H); **Giuseppe Fornarini:** Astellas, Janssen, Pfizer, Bayer, MSD, Merck (SAB), Astellas, Janssen, Bayer (travel expenses); **Giuseppe Luigi Banna:** Astellas, AstraZeneca (personal fees). The other authors indicated no financial relationships.

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Author Contributions

Conception/design: G.L.B., G.F., U.B. Provision of study material or patients: M.M., S.E.R, M.C., H.L., L.F., T.G., D.B., A.D., P.E. Collection and/or assembly of data: A.Msaki., V.M., B.B., V.L., F.V. Data analysis and interpretation: G.L.B., P.R., O.C., A.M., E.F.G., V.C., U.D.G. Manuscript writing: P.R., G.L.B. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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