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European Association of Urology

A Phase 2 Randomized Open-label Study of Oral Darolutamide Monotherapy Versus Androgen Deprivation Therapy in Men with Hormone-sensitive Prostate Cancer (EORTC-GUCG 1532)

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Article info

Article history:
Received 30 October 2023
Received in Revised form
24 December 2023
Accepted 10 January 2024
Available online 24 January 2024

Associate Editor:
Guillaume Ploussard

Keywords:
Prostate cancer
Hormone therapy
Antiandrogen
Darolutamide
Gonadotropin-releasing hormone analog
Health-related quality of life

Abstract

Background and objective: Darolutamide is an androgen receptor inhibitor that increases overall survival in combination with androgen deprivation therapy (ADT) in patients with metastatic hormone-sensitive and nonmetastatic castration-resistant prostate cancer (PCa). This phase 2 study assessed the efficacy and safety of darolutamide as monotherapy without ADT in patients with eugonadal testosterone levels.

Methods: This was a 24-wk, open-label, randomized study of patients with hormone-sensitive, histologically confirmed PCa requiring gonadotropin-releasing hormone (GnRH); an Eastern Cooperative Oncology Group performance status score of 0/1; and life expectancy >1 yr. All patients received darolutamide 600 mg bid or a commercially available GnRH analog. The primary endpoint is a prostate-specific antigen (PSA) response, defined as a $\geq$80% decline at week 24 relative to baseline in the darolutamide study arm. The GnRH arm is used as an internal control. The secondary endpoints included changes in T levels, safety/tolerability, and quality of life.

Key findings and limitations: Among 61 men enrolled, the median (range) age was 72 yr (53–86 yr); 42.6% of them had metastases. In the darolutamide arm, the evaluable population with available PSA values at baseline and week 24 consisted of 23 patients. Twenty-three (100%) evaluable darolutamide patients achieved a PSA decline of >80% at week 24 (primary endpoint), with a median (range) decrease of –99.1% (–91.9%, –100%). Serum T levels increased by a median (range) of 44.3 (5.7–144.0) at week 24, compared with baseline. In the darolutamide arm, 48.4% of men reported drug-related adverse events (AEs; mostly grade 1 or 2). The most frequent treatment-emergent AEs included gynecomastia (35.5%), fatigue (12.9%), hot flush (12.9%), and hypertension (12.9%). Health-related quality of life measures are descriptive, and GnRH arm results will be presented as an internal reference.

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https://doi.org/10.1016/j.euo.2024.01.009

Conclusions and clinical implications: Darolutamide monotherapy was associated with a significant PSA response in nearly all men with hormone-naïve PCa. Testosterone-level changes and most common AEs (gynecomastia, fatigue, hypertension, and hot flush) were consistent with potent androgen receptor inhibition.

Patient summary: In this study, we report the first use of darolutamide, a novel antiandrogen, as monotherapy without androgen deprivation therapy (ADT). The study shows that darolutamide induce a profound suppression of prostate-specific antigen in all patients, with a safety profile different from that of ADT.

1. Introduction

The standard of care systemic treatment for prostate cancer (PCa) is androgen deprivation therapy (ADT) using gonadotropin-releasing hormone (GnRH) analogs or surgical castration [1]. ADT is associated with well-known short- and long-term side effects [2].

In contrast to ADT, nonsteroidal antiandrogens directly inhibit the androgen receptor (AR) without lowering testosterone and are associated with increased serum testosterone levels. Consequently, nonsteroidal antiandrogens have a different side-effect profile, notably gynecomastia. In Europe, bicalutamide is the only antiandrogen registered as monotherapy at a daily dose of 150 mg. The third-generation antiandrogens enzalutamide and apalutamide were tested as monotherapy in small phase II trials but are not yet registered in that indication [3–6]. More recently, a larger phase II trial, EMBARK, compared ADT with enzalutamide monotherapy and demonstrated that enzalutamide increases metastasis-free survival compared with ADT, yet with an increase in cardiovascular toxicity and significant gynecomastia [7].

Darolutamide is a nonsteroidal AR antagonist with a unique molecular structure, distinct from other AR antagonists [8]. In mouse models, darolutamide showed negligible blood-brain barrier penetration [9]. In combination with ADT, darolutamide increases overall survival (OS) and other oncological endpoints in newly diagnosed metastatic hormone-naïve PCa in combination with docetaxel and in high-risk nonmetastatic castration-resistant PCa [10,11]. Interestingly, in both trials, darolutamide showed only a modest increase in side effects compared with placebo.

We report the first study with darolutamide monotherapy in a phase II randomized noncomparative trial versus GnRH analogs.

2. Patients and methods

EORTC-1532 is an open-label, noncomparative, controlled, randomized phase II study (NCT02972060). The experimental arm received darolutamide at the dose of 600 mg (2×300-mg tablets) bid for a daily dose of 1200 mg. The arm receiving GnRH is included as an internal control and receives any commercially available GnRH analog at the registered dose. The study's primary objective is to demonstrate that $\geq$80% of the patients in the darolutamide arm achieve a prostate-specific antigen (PSA) response at 24 wk. Patients were randomized 1:1 and stratified for the type of GnRH analogs (agonist vs antagonist), patient's disease status at presentation (metastatic measurable vs metastatic nonmeasurable vs nonmetastatic), and age ($\geq$70 vs <70 yr). Patients with a clinical benefit at week 24 continue to receive darolutamide at the investigator's discretion until disease progression or occurrence of unacceptable toxicity.

The main inclusion criteria were the following: histologically confirmed PCa (all stages) in those for whom continuous ADT is indicated for a minimum period of 24 wk, stage M0 or M1 with four or fewer confirmed nonvisceral metastatic lesions, asymptomatic for metastatic PCa, baseline total testosterone $\geq$8 nmol/l or 230 ng/dl, and two subsequent PSA values $\geq$2 ng/ml, done in the past 3 mo (before enrolment) with a minimum of 2 wk between the two, with the second being equal to or higher than the first. The main exclusion criterion is previous or current hormonal therapy intending to treat PCa disease (surgical castration or other hormonal manipulation, eg, luteinizing hormone-releasing hormone [LHRH] agonists, LHRH antagonists, antiandrogens, estrogens, and 5α-reductase inhibitor). PSA, testosterone, and side effects were collected at baseline and at weeks 4, 8, 12, 18, and 24. Health-related quality of life (HRQoL) assessment was based on the European Organisation of Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-PR25, and Aging Male Symptoms (AMS) questionnaires [12–14].

The primary endpoint is PSA response assessed at week 24, defined as a $\geq$80% decline in PSA measurement taken at week 24 relative to baseline in the darolutamide study arm. The PSA response rate at 24 wk is estimated in each arm separately by binomial proportions; exact confidence intervals (CIs) will be provided at the 90% two-sided confidence level. The study will be positive if the point estimate of the 24-wk PSA response rate is >86.2% ($\geq$97/112 responders). A first interim analysis was planned on 34 evaluable patients in the experimental arm (30.4% information). The trial would be stopped for futility if the point estimate of PSA response rate at 24 wk is $\leq$72.5% (ie, $\leq$24/34 responders). The key secondary endpoints include the change in hormone treatment–related symptom scale of the EORTC QLQ-PR25 at 24 wk compared with baseline in the darolutamide study arm and PSA complete response rate at 24 wk defined as a $\geq$90% decline in PSA measurement at week 24 relative to the measurement taken at baseline. Safety was reported according to NCI-CTC version 4.03. The pre-

sent analysis consists of a descriptive analysis of PSA and testosterone levels at baseline and 24 wk from randomization, primary (≥80%) and secondary (≥90%) endpoints of PSA response decline at week 24 relative to baseline, an overall summary of adverse events (AEs), and HRQoL measures. Group differences and within-patient change in QLQ-C30 and QLQ-PR25 scale scores of at least 10 points (with 5 points as sensitivity) were considered clinically meaningful [15,16].

3. Results

3.1. Patients' characteristics

Sixty-one patients were randomized, 32 in the darolutamide arm and 29 in the GnRH arm. The study CONSORT diagram is annexed (Fig. 1). The patient's baseline characteristics are summarized in Table 1. At the time of database lock, the median follow-up was 22.1 (interquartile range

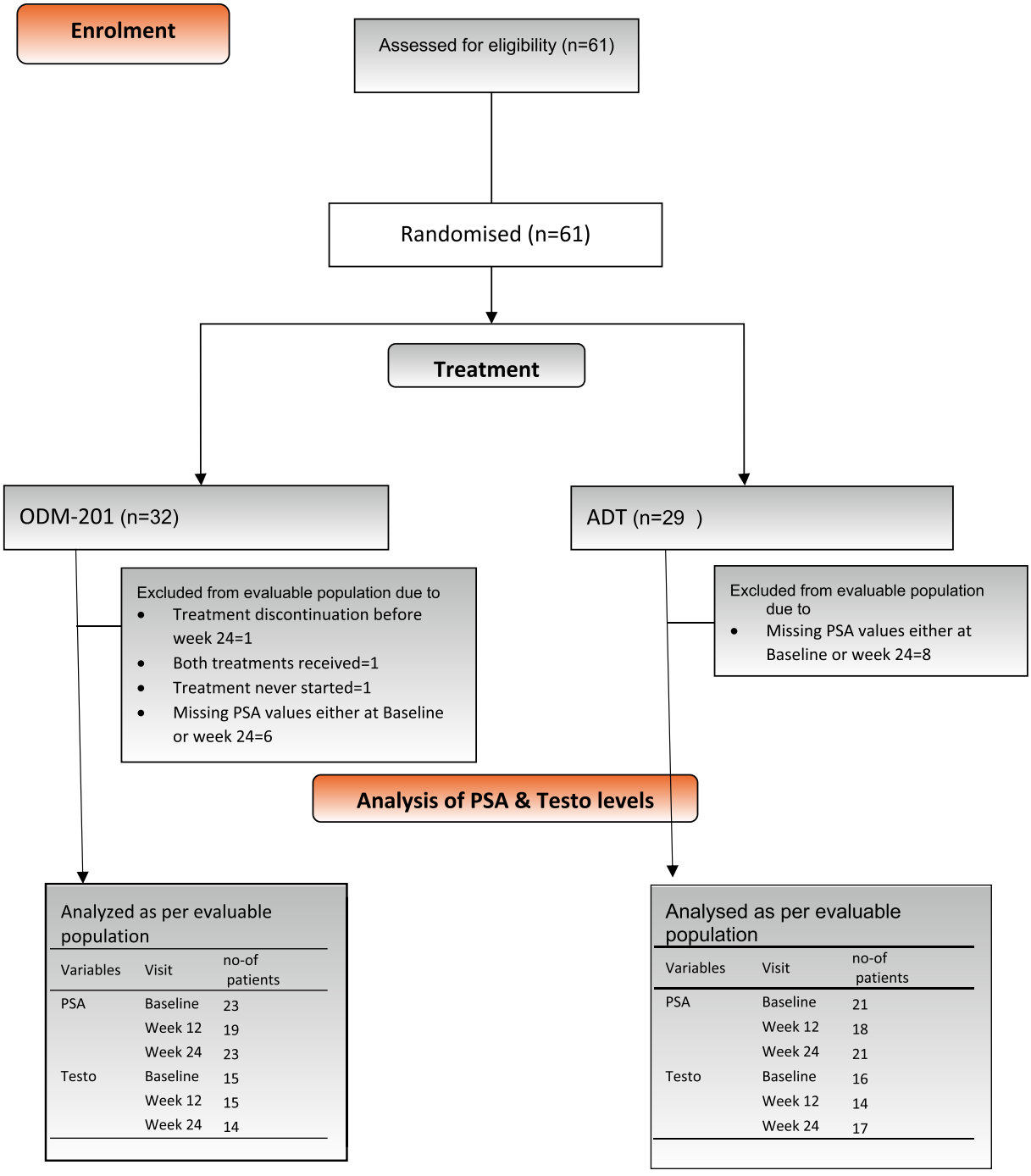

Fig. 1 – Study CONSORT diagram. ADT = androgen deprivation therapy; PSA = prostate-specific antigen; Testo = testosterone.

Table 1 – Patient characteristics at baseline

	Darolutamide (n = 32)	GnRH analog (n = 29)
Age (yr), median (IQR)	72.0 (64.0–77.5)	74.0 (68.0–76.0)
Age ≥70 yr (%)	56.2	62.1
Status at randomization, *N* (%)		
Gleason (<7/7/>7)[a]	4/14/14 (12.5/43.8/44.8)	5/8/13 (17.2/27.5/44.7)
TNM metastatic stage, *N* (%)		
N1	11 (34.4)	3 (10.3)
M0	18 (56.3)	17 (58.6)
M1a (nonregional lymph nodes)	4 (12.5)	1 (3.4)
M1b	6 (18.8)	8 (27.6)
M1c	1 (3.1)	0 (0.0)
GnRH analog, *N* (%)		
Agonist		22 (75.9)
Antagonist		7 (24.1)
ECOG performance status 0/1 (%)	84.4/15.6	93.1/6.9
Prior treatment, *N* (%)		
Prostate radiotherapy	18 (58)	21 (72)
(Neo)adjuvant ADT	6 (18.8)	7 (24.1)

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; GnRH = gonadotropin-releasing hormone; IQR = interquartile range; TNM = tumor, node, metastasis.
[a] Three Gleason score missing GnRH arm.

Table 2 – Frequency of adverse events reported for the safety population and during the treatment period up to the clinical cutoff date

	Darolutamide	ADT
During randomized treatment (n = patients starting treatment), *N* (%)	n = 31	n = 29
At least one grade ≥1 AE	21 (67.7)	16 (62.1)
At least one grade ≥3 AE	3 (9.7)	2 (6.9)
At least one grade ≥1 TRAE	15 (48.4)	11 (37.9)
At least one grade ≥3 TRAE	1 (3.2)	
Most common grade ≥1 AE, *N* (%)		
Gynecomastia	11 (35.5)	
Fatigue	4 (12.9)	3 (10.3)
Hot flashes	4 (12.9)	11 (37.9)
Cholesterol high	3 (10.3)	3 (10.3)
Hypertension	4 (12.9)	2 (6.9)
Most common grade ≥1 TRAE, *N* (%)		
Gynecomastia	9 (29)	
Fatigue	4 (12.9)	3 (10.3)
Hot flashes	4 (12.9)	10 (34.5)
Breast Pain	2 (6.5)	
Most common grade ≥3 TRAE, *N* (%)		
Serum amylase increased	1 (3.2)	

ADT = androgen deprivation therapy; AE = adverse event; TRAE = treatment-related adverse events as per local investigator assessment.

[IQR] 15.5–25.0) mo for patients receiving darolutamide and 24.8 (IQR 17.2–26.0) mo for patients receiving a GnRH analog. At the clinical data cutoff, 18 (51%) patients still received darolutamide and seven (24.1) received a GnRH analog. The median treatment duration on darolutamide was 29.1 (25.7–77.0) mo, with 29 (93.5%) patients continuing beyond 24 wk. The reasons for darolutamide discontinuation were completing the initial treatment plan in seven, progressive disease in three, patient's decision in two, and other reasons in two patients. The reasons for GnRH discontinuation were completing the initial treatment plan in 16 patients, progressive disease in five patients, and patient's decision in one patient. The study was stopped for poor recruitment after 61 randomized patients, and 100% of the 32 darolutamide patients reached the primary endpoint.

3.2. *Safety*

All AE data are reported in Table 2 for the safety population and during the treatment period up to the clinical cutoff date. In total, 21 (67.7%) of the patients in the darolutamide arm and 18 (62.1%) in the GnRH analog arm reported a grade ≥1 AE. Grade ≥3 AEs were reported in three (9.7%) patients in the darolutamide arm and two (6.9%) in the GnRH arm. AEs occurring at a frequency of ≥10% in the darolutamide arm were fatigue (12.9%), hypertension (12.9%), hot flushes (12.9%), and gynecomastia (35.5%). All but one of the gynecomastia and one hypertension AE were of grade 1. In the GnRH arm, AEs occurring at frequency ≥10% were fatigue (10.3%), high cholesterol (10.3%), and hot flushes (37.9%). There were no grade 4 and 5 toxicity reports. Serious AEs (grade ≥1) were reported in three (9.7%) of the patients in the darolutamide arm and one (3.4%) in the GnRH arm.

3.3. *PSA endpoints*

PSA values were available at baseline and 24 wk for 23 patients in the darolutamide arm and 21 in the GnRH arm. The median (range) value of PSA at baseline was 8.9 (2.2–333.8) ng/ml in the darolutamide arm and 7.8 (2.2–37.4) ng/ml in the GnRH arm. PSA evolution over the trial is presented in Figure 2. The primary endpoint of achieving a ≥80% decrease in PSA from baseline at week 24 was reached in 100% (90% two-sided confidence level [CI] 87.8–100%) of patients in the darolutamide arm and 85.7% (90% CI 67.1–90.6%) in the GnRH arm. The secondary endpoint of achieving a ≥90% decrease in PSA from baseline at week 24 was reached in 100% (90% CI 87.8–100%) of patients in the darolutamide arm and 81.0% (90% CI 61.6–93.2%) in the GnRH arm.

3.4. *Testosterone endpoint*

In the darolutamide arm, the median (range) value of testosterone was 413 (209.0–1183.0) ng/dl at baseline and increased by 43.3% (5.7–144.0%) to a median (range) of 595.0 (260.0–1500.0) ng/dl at week 24. In the GnRH arm, the median (range) value of testosterone was 333.0 (210.9–844.0) ng/dl at baseline and decreased by –96.0% (–99.6% to –80.8%) to a median (range) of 12.9 (1.2–52.8) ng/dl at week 24. Figure 3 shows the absolute change in testosterone values from baseline over time for the two arms.

3.5. *HRQoL data endpoint*

Compliance with completing questionnaires per assessment time point ranged from 89.5% at baseline to 47.1% at week 24. EORTC QLQ-C30, QLQ-PR25, and AMS baseline scores and change scores at 24 wk from the baseline are reported in Table 3. For the QLQ-C30, a mean difference of >10 points between arms was observed in the insomnia scale (higher in the darolutamide arm) at baseline. At 24 wk, a mean difference in change scores of >10 points was observed in the diarrhea scale, with worse mean scores reported in the

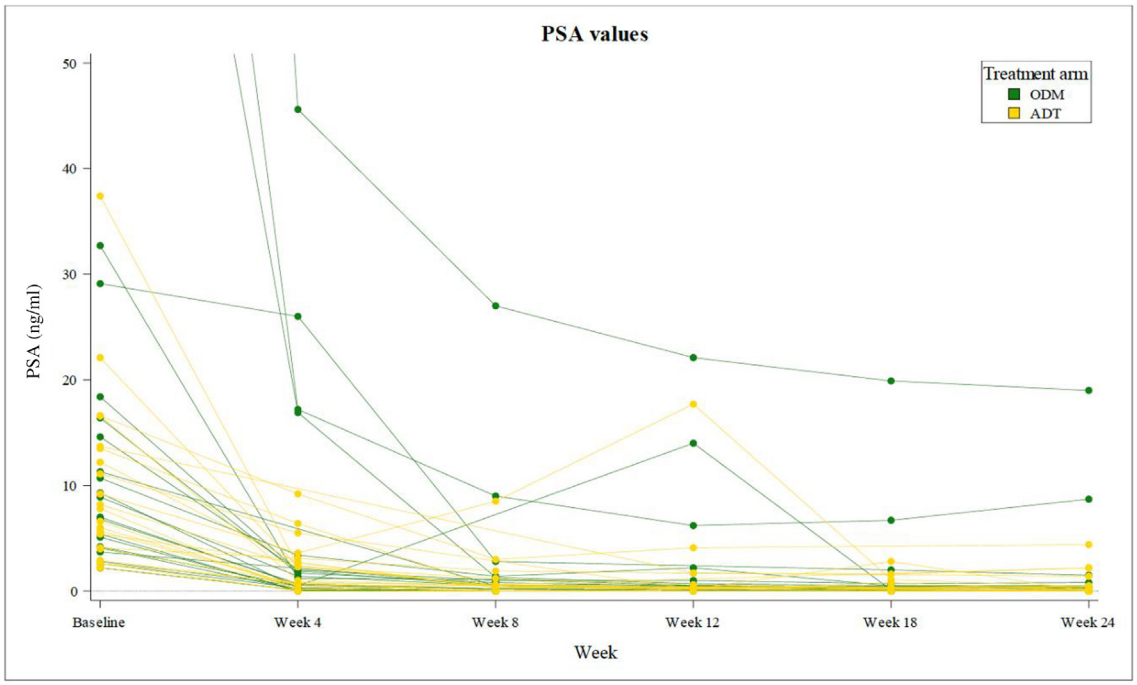

Fig. 2 – PSA evolution (in ng/ml) over the trial for patients receiving darolutamide (green) and ADT (yellow). ADT = androgen deprivation therapy; PSA = prostate-specific antigen.

GnRH arm. For the QLQ-PR25, the most significant mean difference scale scores between treatment arms were observed in the incontinence aid scale (difference of 17.6 points). However, more patients have received radiotherapy in the GnRH arm (72%) than in the darolutamide arm (58%), and the sample size was minimal (n = 17 in total). A mean difference in change scores of >10 points was observed in the sexual functioning scale, but the sample size was also minimal (n = 13 in total). The mean scores of all subscales of the AMS, including the total score, were similar in both treatment groups.

For the HRQoL scale of interest, that is, the hormone therapy symptom scale of the EORTC QLQ-PR25, a lower mean change score (fewer problems) at week 24 from baseline was observed in the darolutamide arm. However, the treatment difference in the mean change score did not meet the clinically meaningful threshold of 10 points. Figure 4 depicts the least-square means profile plot for the hormone therapy symptom change scores from baseline (99% CI) to week 24. Increasing mean change scores are observed in both arms (except at week 4 in the darolutamide arm). However, systematically lower mean change scores (lesser problems) were observed in the darolutamide arm over time. Based on changes in the hormone therapy symptom scores at week 24 from the baseline, patients were categorized as improved (+≥10 points), stable (absolute change <10 points), or deteriorated (−≥10 points). A second analysis was performed with a ±5 point threshold. Figure 5 reports the different proportions. Only patients with a valid quality of life form at baseline and week 24 were included in this analysis (n = 22). Most of the patients had clinically meaningful deterioration in both treatment arms. In the deteriorated category, there were 63.6% in the darolutamide and 77.3% in the GnRH arm (10-point rule); similar results are observed with the 5-point rule: –63.6% in the darolutamide and 86.4% in the GnRH arm.

4. Discussion

Combining ADT with abiraterone, enzalutamide, apalutamide, or darolutamide is the standard systemic treatment for very-high-risk localized and metastatic PCa [2]. Since testosterone is ubiquitous, ADT causes AEs [17]. Short-term AEs include loss of libido, muscle weakness, hot flashes, and emotional liability. Long-term AEs include sarcopenic obesity and lipid changes leading to an increased risk of cardiovascular disease, loss of bone mineral density, increased risk of fractures, and cognitive decline [17].

With their more selective mode of action, AR antagonists represent a valid alternative to ADT to avoid these side effects. The European Medicines Agency has granted market authorization for monotherapy with bicalutamide (oral) 150 mg/d as an alternative to ADT for patients with locally advanced PCa. Monotherapy with bicalutamide was indeed shown to be equivalent to ADT in a pooled analysis of two randomized control trials in nonmetastatic PCa [18]. A general trend toward better quality of life was also observed, favoring bicalutamide 150 mg, especially in sexual appetence and fitness [18]. Bicalutamide also increases OS in combination with radiotherapy in patients with locally advanced disease and a biochemical recurrence after radical prostatectomy [19,20].

Apalutamide was tested in a randomized phase 2 study that compared, in 90 patients with biochemically recurrent PCa, apalutamide (240 mg/d) alone, apalutamide plus ADT,

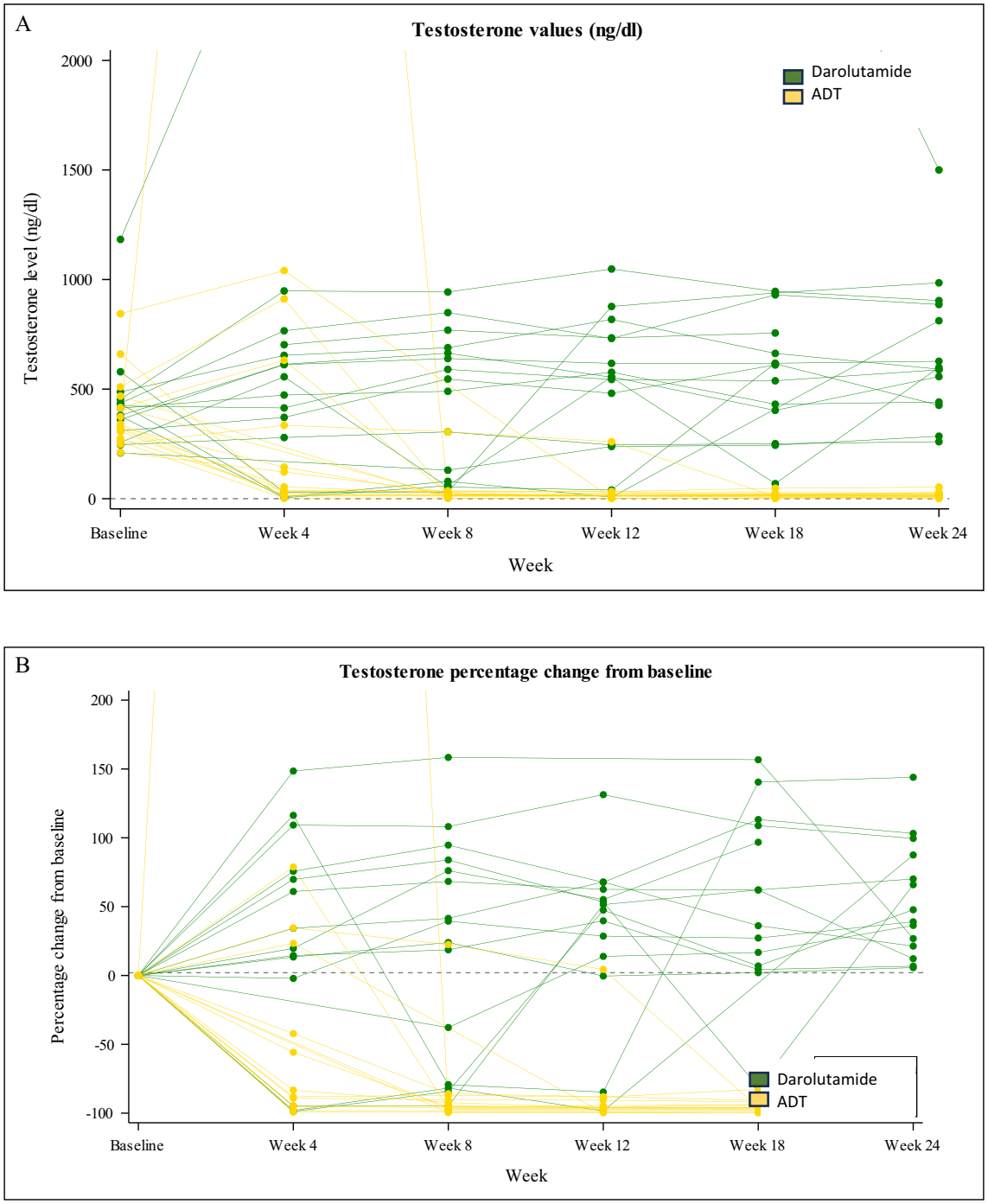

Fig. 3 – Evolution of (A) testosterone level and (B) testosterone percentage change from baseline over time for darolutamide (green) and ADT (yellow). ADT = androgen deprivation therapy.

or ADT alone for 12 mo [3]. There was no significant difference in the primary endpoint and the mean change from baseline to 12 mo in the FACT-P total score. The median time to PSA progression was similar to that with apalutamide and ADT monotherapies. Enzalutamide was tested as monotherapy in a single-arm phase 2 study in 67 patients with hormone-sensitive PCa for whom hormone therapy was indicated [4–6]. At week 25, 92.5% of the patients achieved a PSA decline of ≥80% from baseline [6]. The most reported treatment-emergent AEs up to week 25 were gynecomastia, nipple pain, fatigue, and hot flush, all of which were of mild to moderate severity. EMBARK has randomized 1068 patients with a high-risk biochemical recurrence after local treatment to enzalutamide + leuprolide acetate, placebo + leuprolide, or enzalutamide monotherapy [7]. The metastasis-free survival for enzalutamide monotherapy was statistically superior to that for leuprolide alone (hazard ratio [HR] 0.63; 95% CI 0.46–

Table 3 – Descriptive summaries of QLQ-C30 and QLQ-PR25 and AMS scale scores at baseline and change scores at week 24 from baseline

	Darolutamide (*N* = 27)		ADT (*N* = 26)	
	Baseline Mean (SD)	Change at week 24 from baseline Mean (SD)	Baseline Mean (SD)	Change at week 24 from baseline Mean (SD)
EORTC QLQ-C30 (n = 19–20 per arm)				
Physical functioning	92.33 (10.43)	−0.83 (9.39)	89.67 (19.64)	−2.22 (10.38)
Role functioning	92.50 (16.64)	0.00 (19.25)	92.50 (17.50)	00.00 (14.21)
Emotional functioning	82.28 (16.52)	1.67 (6.45)	80.83 (23.59)	6.25 (23.87)
Cognitive functioning	98.25 (5.26)	−7.78 (12.39)	88.33 (21.01)	2.78 (11.96)
Social functioning	96.49 (8.92)	−2.22 (16.51)	94.17 (13.55)	−2.78 (13.91)
Fatigue	16.39 (19.87)	1.74 (15.14)	13.33 (18.24)	0.00 (15.71)
Nausea/vomiting	1.67 (7.45)	−1.04 (9.56)	0.83 (3.73)	−1.39 (4.81)
Pain	10.00 (14.71)	1.04 (15.48)	9.17 (21.27)	0.00 (10.05)
Dyspnea	5.00 (12.21)	0.00 (12.17)	6.67 (17.44)	−5.56 (23.92)
Insomnia	21.67 (27.09)	−8.33 (14.91)	10.00 (21.90)	−2.78 (30.01)
Appetite loss	1.67 (7.45)	−2.08 (8.33)	3.33 (10.26)	−2.78 (9.62)
Constipation	12.28 (19.91)	−4.44 (17.21)	6.67 (17.44)	0.00 (24.62)
Diarrhea	5.26 (12.49)	0.00 (0.00)	6.67 (17.44)	11.11 (21.71)
Financial problems	1.75 (7.65)	2.22 (8.61)	6.67 (17.44)	−2.78 (9.62)
Global health status/QoL	82.46 (14.41)	−3.33 (12.12)	76.25 (14.12)	−9.03 (27.11)
EORTC QLQ-PR25 (n = 8–22 per arm)				
Sexual activity	40.15 (24.48)	−9.98 (22.42)	28.99 (24.21)	−8.97 (14.62)
Sexual functioning	58.10 (15.66)	−12.50 (23.57)	50.00 (30.90)	0.00 (41.67)
Urinary symptoms	16.40 (15.49)	1.19 (17.79)	22.11 (16.47)	−5.27 (8.77)
Bowels symptoms	1.59 (3.35)	0.52 (5.67)	3.79 (8.02)	1.92 (6.04)
Hormonal symptoms	11.11 (10.57)	5.88 (9.91)	8.33 (7.81)	8.33 (9.89)
Incontinence aid	8.33 (15.43)	16.67 (19.25)	25.93 (36.43)	−13.33 (18.26)
AMS (n = 21–22 per arm)				
Somatic	10.76 (4.93)	0.06 (2.38)	10.81 (4.37)	0.73 (3.04)
Psychological	6.33 (2.74)	0.29 (1.86)	6.33 (3.10)	1.09 (4.18)
Sexual	11.52 (4.69)	−0.82 (6.87)	11.62 (5.24)	−1.45 (4.08)
Total score	28.62 (10.68)	−0.47 (8.81)	28.76 (8.83)	0.36 (8.10)

ADT = androgen deprivation therapy; AMS = Aging Male Symptoms; EORTC = European Organisation of Research and Treatment of Cancer; HRQoL = health-related quality of life; *n* = range of observed sample size for scales in each treatment arm; QoL = quality of life; SD = standard deviation.
QLQ-C30/PR25 scale scores range from 0 to 100; higher scores for the functioning and global health scales correspond to better functioning and HRQoL, while high scores in the symptom scales correspond to worsening symptom burden. Higher AMS scale scores represent greater severity of symptoms.

0.87; $p = 0.0049$). Interim OS data also favored enzalutamide monotherapy (HR 0.78; 95% CI 0.52−1.17; $p = 0.2304$). The proportion of grade ≥3 events is numerically superior with enzalutamide monotherapy (50%) to that with ADT (42%). However, the toxicity profile is different. Hot flushes were reported in 57% of patients on ADT versus 22% on enzalutamide, while gynecomastia was reported in 9% of patients on ADT versus 44.9% on enzalutamide. More importantly, the rates of cognitive and memory impairment and ischemic heart disease almost double with enzalutamide versus ADT (14.1 vs 6.5 and 9 vs 5.6, respectively). The patient-reported outcome scores remained stable throughout the trial for most patients in all groups, suggesting maintenance of the high baseline HRQoL and low baseline symptoms across all groups, with no clinically meaningful differences [21].

Darolutamide has a different structure from enzalutamide and apalutamide [8]. It has shown negligible blood-brain barrier penetration in animal models and does not reduce models' cerebral blood flow in 23 male volunteers [22,23]. In combination with ADT, darolutamide increased OS in patients with high-risk nonmetastatic castration-resistant PCa and patients with hormone-naïve PCa, combined with docetaxel [10,11]. In both trials, darolutamide caused a lower rate of AEs than placebo.

Our study assessed the safety and efficacy of darolutamide as monotherapy. Patients were randomized versus GnRH alone. The latter was used as a historical control, with no intention to perform comparative statistical analyses. There were no specific safety signals. AEs occurring at a frequency of ≥10% in the darolutamide arm were fatigue, hypertension, and gynecomastia, as expected from its mode of action. Darolutamide profoundly affects PSA, with 100% of patients achieving the primary and secondary endpoints of a PSA decrease of ≥80% and ≥90% from baseline at week 24, respectively. In comparison, 85.7% and 81% of the patients receiving a GnRH analog reached the ≥80% and ≥90% endpoints, respectively. The median testosterone level increased by 43.4% at 24 wk. In comparison, testosterone increased by 114.3% at week 25 with enzalutamide monotherapy in the phase II trial of enzalutamide. This difference and its potential consequences will need to be studied further.

Unfortunately, clinically meaningful differences in HRQoL change scores were seen in very few scales across the different HRQoL questionnaires used. Although a lower mean change score was seen for the hormone therapy symptom scale of the EORTC QLQ-PR25 questionnaire, the between-treatment difference in the mean change score did not meet the 10-point clinically meaningful threshold. With the current sample size, assuming a two-sided alpha of 5%, we have <50% power to show a 10-point difference. Therefore, the interpretation of the observed results may also be due to the limited power.

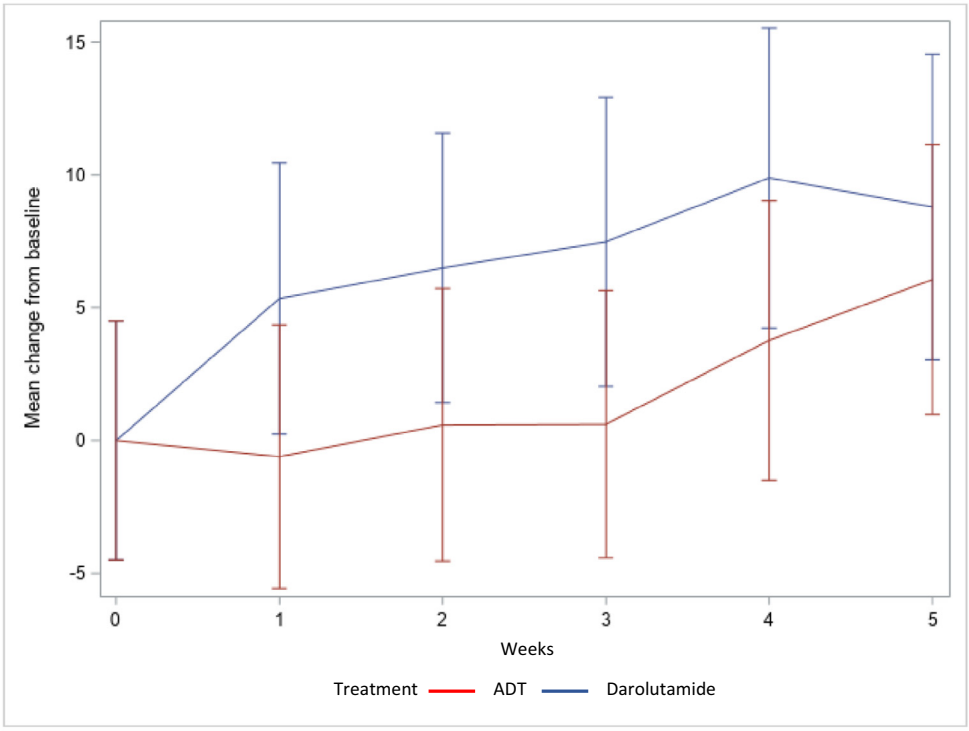

Fig. 4 – Least-square means profile plot for the hormone therapy symptom change scores at different visits from baseline (99% CI). Higher hormone therapy symptom change scores correspond to worsening symptom burden. ADT = androgen deprivation therapy; CI = confidence interval.

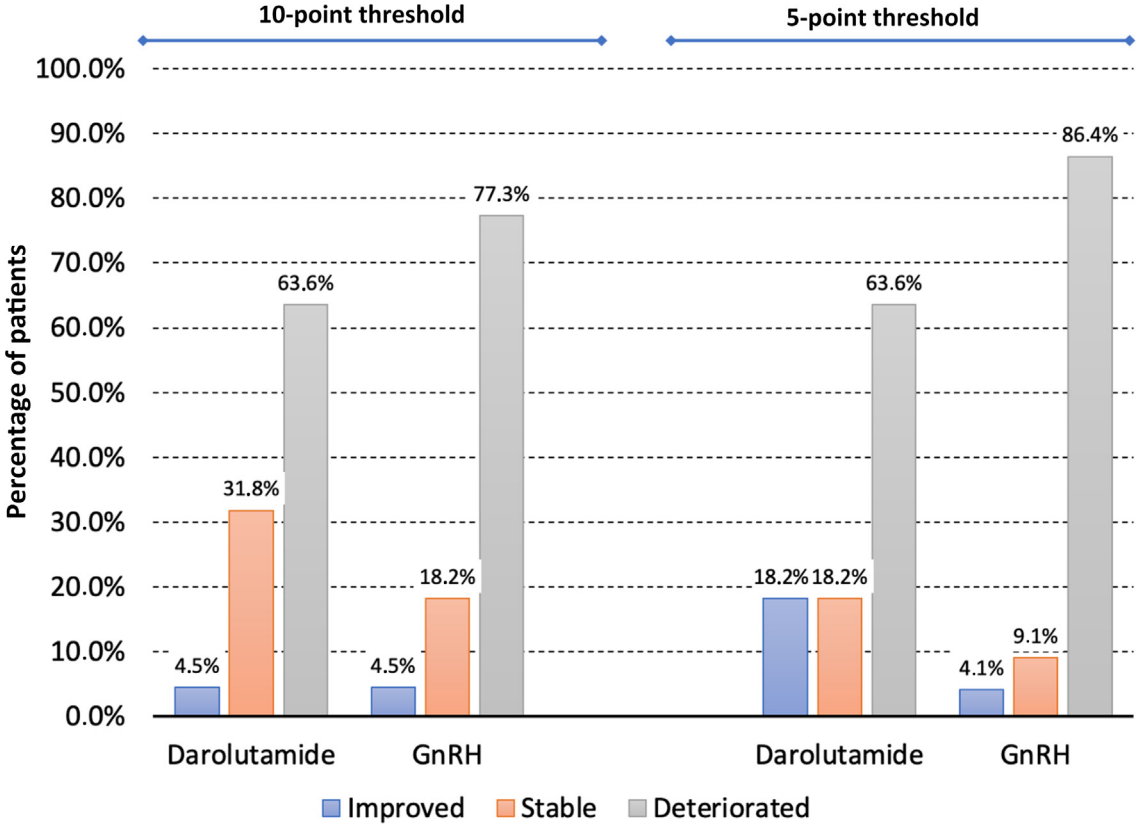

Fig. 5 – Proportion of patients categorized as improved (+≥10 or 5 points), stable (absolute change <10 or 5 points), or deteriorated (–≥10 or 5 points) in the hormone therapy symptom scores at week 24 from baseline. GnRH = gonadotropin-releasing hormone.

We have observed a nonclinically meaningful change of only 1.74 on the fatigue scale of the EORTC QLQ-C30. This differs from the enzalutamide monotherapy trial, which reported a clinically meaningful mean increase of 14.5 points at 24 wk [6]. The mean hormonal symptom score increased by 5.88 points with darolutamide and 8.33 points with the GnRH analogs. The proportion of patients who deteriorated in the hormonal symptom score is numerically inferior with darolutamide than with a GnRH analog. The QLQ-PR25 was designed to measure the impact on HRQoL of a broad range of local and systemic treatments for PCa. The seminal publication highlighted its poor performance for hormonal agents [12]. In the recently published HRQoL results from the relugolix registration trial HERO, the mean hormonal symptom score increased by 10.6 points at week 49 [24]. This suggests that an HRQoL questionnaire tailored for hormonal agents will be needed to understand fully the impact of antiandrogen monotherapy versus GnRH analogs. Here, we have tried using the AMS score, developed to determine the severity of aging males' symptoms, that is, in comparison with the standard population [14]. Unfortunately, AMS does not help differentiate the two classes of agents. In cases where the standard HRQoL questionnaires may not be sensitive to relevant treatment-related symptoms, item libraries may be considered for a more tailored and flexible HRQoL assessment [25].

A potential theoretical advantage of antiandrogen monotherapy is a better preservation of sexual function. Two domains of the QLQ-PR25 investigate sexual health. The sexual activity domain comprises two compulsory questions: "To what extent were you interested in sex?" and "To what extent were you sexually active (with or without intercourse)?" [12]. We observed a similar deterioration in both groups in the sexual activity score at week 24: –9.98 points in the darolutamide arm (n = 22) and –8.97 points in the GnRH arm (n = 22), not reaching the accepted $\geq$10-point threshold for clinical importance. The second domain, the sexual functioning domain, is answered by patients only "if they have been sexually active over the past 4 weeks". Only half of the patients responded to these questions: 12/22 in the darolutamide group and 9/22 in the GnRH group. We observed a 12.50-point deterioration in the GnRH group and no deterioration in the darolutamide group. However, the number of patients is too small to draw any conclusion. The EMBARK trial reported a benefit in favor of darolutamide for the "time to confirmed clinically meaningful deterioration" of sexual activity. Only 15% of the patients responded to the optional sexual functioning domain questions, invalidating any robust conclusion. This also brings into question the pertinence of the QlQ-PR25 questionnaire to address sexual function in men receiving hormone therapy. As a result, it may miss some essential differences between different treatment classes.

5. Conclusions

In conclusion, we demonstrated that treatment with darolutamide as monotherapy induces a significant PSA response in nearly all men with hormone-naïve PCa. Testosterone-level changes and most common AEs (gynecomastia, fatigue, hypertension, and hot flush) were consistent with potent AR inhibition. Further studies will be needed to position this indication in the PCa treatment landscape.

Author contributions: Bertrand F. Tombal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtaining funding: Tombal.
Administrative, technical, or material support: Krzystyniak.
Supervision: Tombal, Loriot.
Other: None.

Financial disclosures: Bertrand F. Tombal certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Bertrand F. Tombal: honoraria—Amgen, Astellas Pharma, Bayer, Ferring, Janssen, Myovant Sciences, Pfizer, and Sanofi; consulting or advisory role—Astellas Pharma, Bayer, Ferring, Janssen, Myovant Sciences, Pfizer/Astellas, Sanofi, Steba Biotech, and Takeda; speakers' bureau—Amgen, Astellas Pharma, and Janssen; research funding—Ferring (Inst); expert testimony—Steba Biotech; and travel, accommodations, expenses—Amgen, Astellas Pharma, Bayer, Ferring, Janssen, and Sanofi. Fernando López-Campos: no relationships to disclose. Piet Ost: consulting or advisory role—Astellas Pharma, Bayer, Curium Pharma, Janssen-Cilag, Novartis, and Telix Pharmaceuticals; research funding—Bayer (Inst) and Varian Medical Systems (Inst); and travel, accommodations, expenses—Ferring. Thierry Andre Roumeguere and Bernardo Herrera-Imbroda: no relationships to disclose. Lionel A. D'Hondt: consulting or advisory role—Bayer and Janssen. Magali Quivrin: no relationships to disclose. Paolo Gontero: honoraria—Astellas Oncology, Janssen, and Photocure; speakers' bureau—Medac; and research funding—Ferring. Salvador Villà, Hussein Mustafa Khaled, Beatrice Fournier, Joanna Krzystyniak, Yassin Pretzenbacher, and Jammbe Musoro: no relationships to disclose. Yohann Loriot: consulting or advisory role—Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Immunomedics, Janssen, Janssen (Inst), Loxo/Lilly, MSD Oncology, MSD Oncology (Inst), Pfizer/EMD Serono, Roche, Seagen, and Taiho Pharmaceutical; research funding—Astellas Pharma (Inst), AstraZeneca (Inst), Basilea (Inst), BMS (Inst), Exelixis (Inst), Gilead Sciences (Inst), Incyte (Inst), Janssen Oncology (Inst), Merck KGaA (Inst), MSD Oncology (Inst), Nektar (Inst), Pfizer (Inst), Roche (Inst), Sanofi (Inst), Seagen (Inst), and Taiho

Pharmaceutical (Inst); and travel, accommodations, expenses—Astellas Pharma, AstraZeneca, Janssen Oncology, MSD Oncology, Roche, and Seagen.

Funding/Support and role of the sponsor: This study was supported by the European Organisation of Research and Treatment of Cancer. The EORTC-GUCG 1532 trial was funded by an educational grant from Bayer Healthcare Pharmaceuticals Inc.

Acknowledgments: The authors would like to acknowledge the support of the EORTC 1532 Study Team and the Genito-Urinary Cancers Group. We are grateful to Bayer Healthcare Pharmaceuticals Inc. for supporting this independent EORTC Study.

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