available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Original Article

# Radiotherapy plus Long-term Adjuvant Androgen Deprivation with a Luteinizing Hormone–releasing Hormone Antagonist Versus Agonist in Patients with Very High-risk Localized or Locally Advanced Prostate Cancer: The EORTC GUCG-1414 Phase 3 Randomized Trial

*Thomas Zilli*[a,b,c,*], *Dirk Böhmer*[d], *Andreas Roeder*[e,f], *David Lauffer*[g], *Ana Elena Villafranca Iturre*[h], *Josep Jové Teixidó*[i], *Stéphane Supiot*[j], *Igor Latorzeff*[k], *Piet Dirix*[l], *François-Xavier Otte*[m], *Giulio Francolini*[n], *Thierry Roumeguère*[o], *Jean Marc Simon*[p], *Beatrice Fournier*[q], *Catherine Fortpied*[q], *Pedro C. Lara*[r], *Bertrand Tombal*[s]

[a] *Department of Radiation Oncology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland;* [b] *Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland;* [c] *Faculty of Medicine, University of Geneva, Geneva, Switzerland;* [d] *Klinik für Radioonkologie und Strahlentherapie, Charité-Universitätsmedizin Berlin, Berlin, Germany;* [e] *Copenhagen Prostate Cancer Center, Department of Urology, Center for Cancer and Organ Diseases, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark;* [f] *Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark;* [g] *Department of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland;* [h] *Department of Radiation Oncology, Complejo Hospitalario de Navarra, Pamplona, Spain;* [i] *Department of Radiation Oncology, ICO-Germans Trias Pujol, Badalona, Spain;* [j] *Department of Radiation Oncology, Institut de Cancérologie de L'Ouest, Saint-Herblain, France;* [k] *Department of Radiation Oncology, Clinique Pasteur, Toulouse, France;* [l] *Department of Radiation Oncology, GZA Sint-Augustinus, Antwerp, Belgium;* [m] *Department of Radiation Oncology, Hôpital Universitaire de Bruxelles, Jules Bordet Institute and Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium;* [n] *Department of Radiation Oncology, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy;* [o] *Department of Urology, Hôpital Universitaire de Bruxelles, Jules Bordet Institute and Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium;* [p] *Department of Radiation Oncology, Hôpital Pitié-Salpêtrière, AP-HP, Paris, France;* [q] *EORTC Headquarters, Brussels, Belgium;* [r] *Department of Radiation Oncology, Canarian Comprehensive Cancer Center, San Roque University Hospital, Fernando Pessoa Canarias University, Las Palmas, Spain;* [s] *Department of Urology, Cliniques Universitaires Saint Luc, Brussels, Belgium*

**Article info**

***Article history:***
Received 1 October 2025
Accepted 17 October 2025
Available online 7 November 2025

***Associate Editor:***
Elena Castro, MD

**Abstract**

***Background and objective:*** External beam radiotherapy (EBRT) combined with long-term androgen deprivation therapy (ADT) is standard for high-risk prostate cancer. EORTC 1414 compared ADT with a luteinizing hormone–releasing hormone (LHRH) antagonist (degarelix) or an LHRH agonist in patients who received EBRT.

***Methods:*** Between 2017 and 2023, 379 patients with prostate cancer with at least two high-risk features (prostate-specific antigen [PSA] ≥20 ng/ml, Gleason score ≥8, cN1, or cT3–4) and stage M0 on conventional imaging or stage M1a/b ($n$ = ≤3 lesions) on advanced imaging were enrolled. Patients were randomized to receive 18, 24, or 36 mo of ADT (degarelix, $n$ = 190; LHRH agonist, $n$ = 189) with pelvic EBRT and treatment of all metastases. Owing to low accrual, the primary endpoint was changed from

* Corresponding author. Department of Radiation Oncology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Via Ospedale, 6500 Bellinzona, Switzerland. Tel. +41 91 8118513.
E-mail address: thomas.zilli@eoc.ch (T. Zilli).

https://doi.org/10.1016/j.euo.2025.10.009

***Keywords:***
Prostate cancer
Androgen deprivation
Degarelix
Radiotherapy
Hormone therapy

progression-free survival (PFS) to the PSA nadir response (<0.1 vs ≥0.1 ng/ml) within 6 mo after EBRT.

***Key findings and limitations:*** Median age was 72 yr. A PSA nadir of <0.1 ng/ml was achieved by 60% of patients in the agonist arm and 52% in the degarelix arm (odds ratio 0.73, 95% confidence interval 0.43–1.22; $p = 0.9$). Two-year PFS was 88% in both arms. Adverse events occurred in 89% of agonist and 88% of degarelix patients. Among 41 patients with baseline cardiovascular (CV) disease, four in the agonist arm and one in the degarelix group experienced a CV event. Two CV-related deaths occurred in the agonist arm. Degarelix improved lower urinary tract symptoms, particularly in patients with a baseline International Prostate Symptom Score of ≥13. Limitations include early closure and insufficient power to assess PFS.

***Conclusions and clinical implications:*** Degarelix did not improve the PSA nadir response within 6 mo after EBRT in comparison to LHRH agonists, but was associated with lower incidence of CV events among patients with pre-existing CV disease.



ADVANCING PRACTICE

**What does this study add?**
EORTC 1414 is the first randomized trial to compare degarelix to LHRH agonists in patients receiving external beam radiotherapy for high-risk prostate cancer. While no difference was observed in the prostate-specific antigen nadir response or short-term progression-free survival, the study highlights potential advantages of degarelix in reducing cardiovascular events and improving urinary symptoms, particularly in patients with pre-existing cardiovascular disease or baseline urinary dysfunction. The main limitation is that the study did not complete accrual and was not analyzed as initially designed.

**Clinical Relevance**
EORTC 1414 is the first randomized trial to directly compare adjuvant androgen deprivation with LHRH antagonist (degarelix) with LHRH agonist plus EBRT for high-risk prostate cancer. The study found no significant differences in PSA nadir levels or short-term progression-free survival, but trends in favour of degarelix in specific patient subgroups. Notably, degarelix was associated with less cardiovascular events, especially among those with preexisting cardiovascular disease. Degarelix also alleviated urinary symptoms in patients with lower urinary tract dysfunction. However, the trial's interpretability is limited by its incomplete accrual and deviation from the planned statistical analysis, which may affect the conclusions. These findings suggest that LHRH antagnosit may offer therapeutic advantages in selected patients, warranting further investigation. Associate Editor: Elena Castro, MD.

**Patient Summary**
We compared two types of hormone therapy (degarelix and drugs called luteinizing hormone–releasing hormone agonists) for patients undergoing radiotherapy for prostate cancer. We found no difference in the decrease in PSA (prostate-specific antigen) between the treatments. However, degarelix improved urinary symptoms and reduced heart-related side effects in patients with pre-existing cardiac disease.
**This trial is registered on EudraCT as 2015-005098-19** and on Clinical.Trials.gov as NCT02799706.

## 1. Introduction

External beam radiotherapy (EBRT), in combination with 18–36 mo of androgen deprivation therapy (ADT) with a luteinizing hormone–releasing hormone (LHRH) agonist or antagonist, is a standard treatment option for patients with high-risk localized prostate cancer [1,2]. Unlike LHRH agonists, the LHRH antagonist degarelix immediately suppresses the secretion of testosterone, and thus an initial surge of testosterone is avoided [3,4]. In comparison to LHRH agonists, degarelix delays prostate-specific antigen (PSA) progression in patients with metastatic disease or baseline PSA >20 ng/ml, improves lower urinary tract symptoms (LUTS), particularly in patients with moderate to severe LUTS, and reduce the risk of cardiovascular events (CVEs) in patients with a history of cardiovascular disease [5–10].

On the basis of these considerations, the phase 3b randomized European Organization of Research and Treatment (EORTC) 1414 trial was designed to assess whether degarelix improves progression-free survival (PFS) in comparison to LHRH agonists in patients with very high-risk prostate cancer undergoing EBRT.

## 2. Patients and methods

The detailed inclusion and exclusion criteria, study procedures, radiotherapy techniques, and statistical plan are provided in the Supplementary material.

### 2.1. Study design and participants

EORTC 1414 (ClinicalTrials.gov NCT02799706) was a multicenter, open-label, randomized controlled trial involving patients aged 18–80 yr with histologically confirmed prostate adenocarcinoma and at least two of the following: PSA $\geq$ 20 ng/ml, Gleason score $\geq$8, cN1/pN1, or cT3–4 disease. Patients with stage M0 on standard imaging or oligometastatic stage M1a/b on advanced imaging were eligible. Key exclusion factors were a recent procedure for cardiovascular disease and prior ADT within 6 mo. Patients provided written informed consent before enrollment. The trial was approved by the relevant institutional review boards in all recruiting countries, was sponsored by the EORTC, and was conducted in accordance with good clinical practice guidelines.

### 2.2. Procedures

Participants were randomized 1:1 to receive either degarelix or an LHRH agonist alongside pelvic EBRT delivered according to institutional policy using intensity-modulated or volumetric–modulated arc radiotherapy with conventional fractionation (78–80 Gy in 39–40 fractions) or hypofractionation (60 Gy in 20 fractions). Patients with oligometastatic disease were treated with stereotactic body radiotherapy at a dose of 30 Gy in three fractions, delivered on alternate days. Randomization was stratified by prior clinical CVE (yes vs no), country of treatment, and number of high-risk factors for relapse (2 vs >2). The planned ADT duration (18, 24, or 36 mo) was defined before randomization at the investigator's discretion.

### 2.3. Outcomes

PFS, which was the original endpoint, was defined as the time from randomization to death from any cause, clinical or PSA progression (nadir +2 ng/ml), or initiation of another line of systemic therapy in the absence of disease progression. Patients without any of these events were censored at the date of their last follow-up visit. Because of early closure of the study in February 2023 and insufficient power for assessment of the original primary endpoint, in April 2023 the study coordinators proposed replacement of PFS with a PSA nadir <0.1 ng/ml within 6 mo after EBRT, following ICECaP recommendations [11]. The statistical redesign, including the power calculation, was conducted by a statistician who was independent from the study and only had access to the total number of patients with PSA nadir values available. The EORTC Independent Data Monitoring Committee (IDMC) agreed on the new endpoint in October 2023. None of the study coordinators, the independent statistician, or the IDMC had access to the full study database and to the allocation of patients into either study arm.

Secondary endpoints included the original PFS endpoint, time to next systemic therapy, overall survival (OS), urinary symptoms assessed via the International Prostate Symptom Score (IPSS), and quality of life (QoL) assessed via the EORTC quality of life QLQ-C30 and QLQ-PR25 instruments. The cumulative incidence of CVE was calculated, with censoring patients at the time of switching treatment, date of death, or the last documented visit in the absence of these events. The cumulative incidence of severe urinary tract infection, defined as grade $\geq$3 urinary tract infection according to Common Terminology Criteria for Adverse Events, was calculated with death and initiation of a new systemic anticancer therapy as competing risks, and censoring of patients with none of these events at their last documented visit.

### 2.4. Statistical analysis

The trial was initially designed to demonstrate the superiority of degarelix over LHRH agonists in terms of PFS. The study was designed to have 80% power for detection of a hazard ratio (HR) of 0.708 with a log-rank test at a one-sided type I error of 2.5%, for which the sample size calculated was 885 patients enrolled over a 36-mo period and 264 events. After premature closure of the study and the definition of the new primary endpoint (proportion of patients with a PSA nadir <0.1 ng/ml within 6 mo after EBRT), there was 80% statistical power for detection of a reduction of 15% (from 40% in the control arm to 25% in the experimental arm) with a $\chi^2$ test at a one-sided type I error of 2.5% according to the number of PSA nadir values available in the clinical database at the time of the redesign. Analysis of baseline characteristics and primary and secondary efficacy endpoints was performed in the intention-to-treat (ITT) population. Treatment exposure and safety analyses were conducted in the safety population, which included all individuals who received at least one injection of the allocated treatment. Cumulative incidence curves for clinical CVEs and severe urinary tract infections were generated. Patient-reported outcomes were analyzed in the ITT population. The scales and single items of the EORTC QLQ-C30 and QLQ-PR25 questionnaires were scored and linearly transformed to a scale of 0–100 according to the EORTC manual [12,13]. A higher score for a symptom scale or item indicates a high level of symptomatology/problems; a higher score on a functional scale or global health status/QoL indicates a high level of functioning/QoL. IPSS data over time are reported as the change in score from baseline.

Only the data related to events occurring up to and including the clinical cutoff date of July 31, 2023 were selected for analysis. The database was locked on November 6, 2023. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

## 3. Results

Between November 2017 and January 2023, 379 patients were enrolled (189 in the LHRH agonist arm and 190 in

the degarelix arm) across 38 centers in eight countries. The patient characteristics are reported in Table 1 and Supplementary Figure 1 shows the Consolidated Standards for Reporting of Trials (CONSORT) diagram. Median follow-up was 2.3 yr, and 48% of the patients had more than two risk factors: 62% had PSA >20 ng/ml; 75% had a Gleason score ≥8, 38% had cN1 status, and 84% had stage cT3–4 disease. The median age was 72 (range 47–81) yr.

Of the 370 patients who started treatment (safety population), 150 (41%) completed treatment, 61 (16%) discontinued treatment prematurely, and 159 (43%) were still on treatment at the clinical cutoff date. Nine of 186 patients who started degarelix switched to an LHRH agonist: eight because of adverse events (4.3%) and four within the first 6 mo. EBRT was effectively administered in 97% of the patients: 57% were treated with conventional fractionation (93 in the agonist arm and 110 patients in the degarelix arm), and 39% with moderate hypofractionation (76 in the agonist arm and 65 in the degarelix arm). Nineteen patients (5%) with M1a/b status received metastasis-directed therapy for oligometastatic disease (nine in the agonist arm and ten in the degarelix arm). Despite a slight imbalance in the planned treatment duration between arms, the actual median treatment duration up to the clinical cutoff date was 20.1 mo with LHRH agonists versus 19.4 mo with degarelix. Median treatment duration ranged from 16 to 24 mo, and was 16.8, 23.1, and 23.8 mo with LHRH agonists versus 16.6, 23.6, and 19.8 mo with degarelix for the 18-mo, 24-mo, and 36-mo planned schedules, respectively. The permanent discontinuation rate was 2.7% in both arms.

Post-EBRT PSA nadir values were available for 146/189 patients (77.2%) in the agonist arm and 155/190 (81.6%) in the degarelix arm (Supplementary Table 1). A post-EBRT PSA nadir <0.1 ng/ml at 6 mo was reached in 88 patients (60%) in the agonist arm and 81 (52%) in the degarelix arm (odds ratio 0.73, 95% confidence interval [CI] 0.43–1.22; one-sided $p = 0.9$). PFS events occurred in 61 patients (29 in the agonist arm and 32 in the degarelix arm). The estimated PFS rate at 2 yr was 87.8% (95% CI 81.5–92.1%) in the agonist arm and 88% (95% CI 81.7–92.2%) in the degarelix arm (hazard ratio [HR] 1.00, 95% CI 0.59–1.67; Fig. 1).

Adverse events (AEs) were reported by 89% of patients in the agonist arm versus 88% in the degarelix arm, with comparable rates of grade ≥3 AEs (42% vs 40%). Urinary and gastrointestinal symptoms were well balanced between arms, as illustrated in Table 2. Site injection reactions, all of grade 1 or 2, were more frequent with degarelix than with LHRH agonists (16.7% vs 0.5%). Severe urinary tract infection occurred in four patients (1.1%), two in each treatment arm. The percentage of patients presenting severe treatment-related AEs (grade ≥3) was 21.2% in the agonist

**Table 1 – Patient characteristics**

| | LHRH agonist ($n$ = 189) | Degarelix ($n$ = 190) | Overall cohort ($n$ = 379) |
|---|---|---|---|
| Median age, yr (range) | 72 (48–80) | 72 (47–81) | 72 (47–81) |
| WHO performance status, *n* (%) | | | |
| 0 | 159 (84.1) | 163 (85.8) | 322 (85.0) |
| 1 | 30 (15.9) | 27 (14.2) | 57 (15.0) |
| Median PSA, ng/ml (range) | 23.8 (3.1–380.4) | 25.8 (2.5–340.0) | 24.1 (2.5–380.4) |
| PSA category, *n* (%) | | | |
| ≤20 ng/ml | 72 (38.1) | 73 (38.4) | 145 (38.3) |
| >20 ng/ml | 117 (61.9) | 117 (61.6) | 234 (61.7) |
| Gleason score, *n* (%) | | | |
| <8 | 52 (27.5) | 44 (23.2) | 96 (25.3) |
| ≥8 | 137 (72.5) | 146 (76.8) | 283 (74.7) |
| cT stage, *n* (%) | | | |
| cT1–2 | 24 (12.7) | 35 (18.4) | 59 (15.6) |
| cT3–4 | 165 (87.3) | 155 (81.6) | 320 (84.4) |
| Nodal stage, *n* (%) | | | |
| N0 | 122 (64.6) | 115 (60.5) | 237 (62.5) |
| N1 | 67 (35.4) | 75 (39.5) | 142 (37.5) |
| Metastasis stage M1a/b, *n* (%) | 13 (6.9) | 11 (5.8) | 24 (6.3) |
| Previous CV event, *n* (%) | | | |
| Yes | 19 (10.1) | 22(11.6) | 41 (10.8) |
| No | 170 (89.9) | 168 (88.4) | 338 (89.2) |
| Baseline IPSS, *n* (%) | | | |
| <13 points | 144 (60.4) | 108 (56.8) | 222 (58.6) |
| ≥13 points | 42 (22.2) | 46 (24.2) | 88 (23.2) |
| Data missing | 33 (17.5) | 36 (18.9) | 69 (18.2) |
| Planned ADT duration* | | | |
| 18 mo | 43 (23.4) | 35 (18.8) | 78 (21.1) |
| 24 mo | 52(28.3) | 51 (27.4) | 103 (27.8) |
| 36 mo | 89 (48.4) | 100 (53.3) | 189 (51.1) |
| Median ADT duration received, mo (IQR) [a,b] | | | |
| Overall cohort | 20.1 (16.7–25.7) | 19.4 (15.2–24.6) | 19.5 (15.7–24.9) |
| 18-mo group | 16.8 (16.8–17.8) | 16.6 (16.6–16.8) | 16.8 (16.6–17.7) |
| 24-mo group | 23.1 (16.3–24.0) | 23.6 (12.5–24.3) | 23.6 (15.2–24.2) |
| 36-mo group | 23.8 (14.8–30.6) | 19.8 (13.5–28.6) | 22.2 (14.0–30.4) |

WHO = World Health Organization; PSA = prostate-specific antigen; LHRH = luteinizing hormone–releasing hormone; CV = cardiovascular event; IPSS = International Prostate Symptom Score; ADT = androgen deprivation therapy; IQR = interquartile range.

[a] For patients who started the allocated treatment (184 in the LHRH agonist arm, 186 in the degarelix arm).

[b] ADT delivered up to the cutoff date for this data analysis.

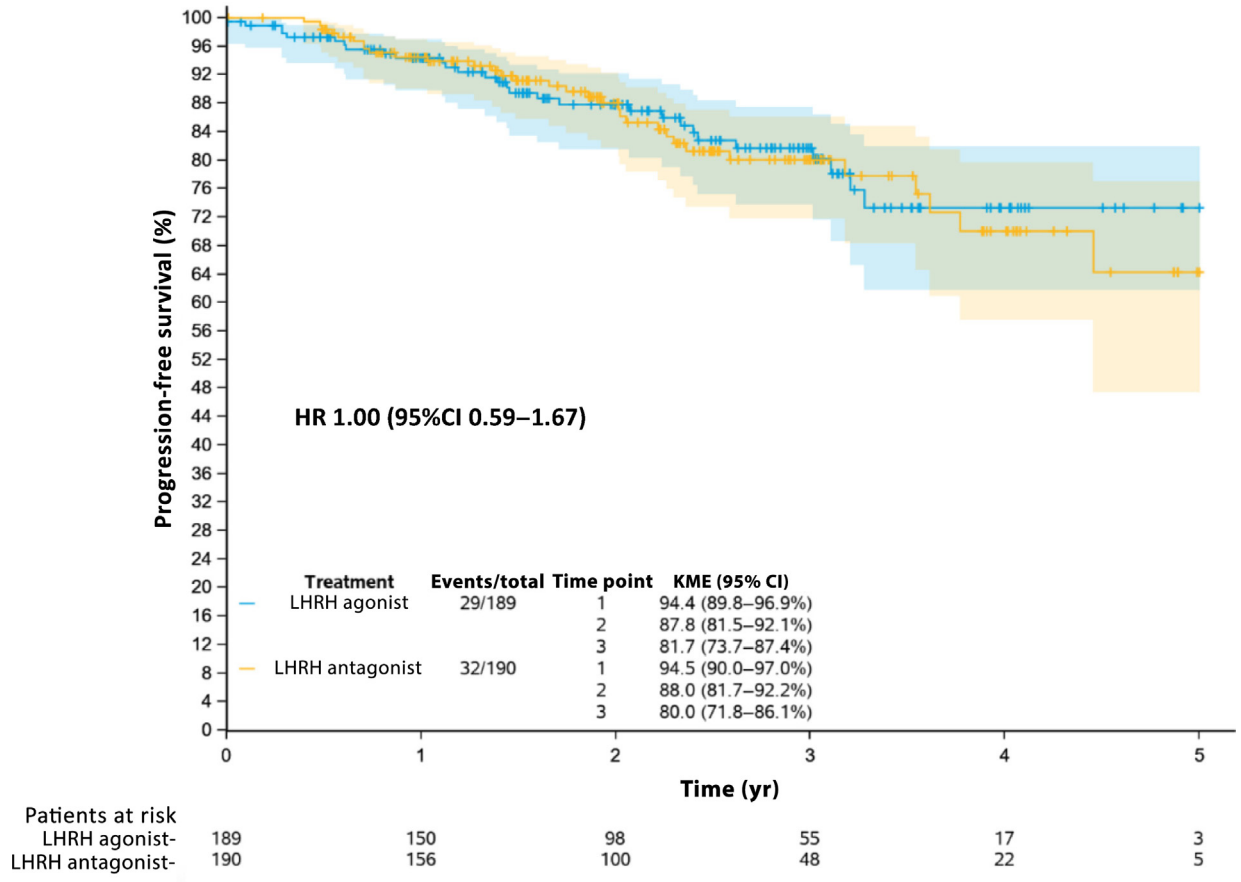


**Fig. 1 – Results for progression-free survival. CI = confidence interval; KME = Kaplan-Meier estimate; LHRH = luteinizing hormone–releasing hormone.**

**Table 2 – Most commonly observed worst toxicities by Common Terminology Criteria for Adverse Events v4.0 grade**

| Toxicity | Patients, *n* (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | LHRH agonist (*n* = 184) | | | | LHRH antagonist (*n* = 186) | | | |
| | Grade 1–2 | Grade 3 | Grade 4–5 | All grades | Grade 1–2 | Grade 3 | Grade 4–5 | All grades |
| Worst grade | 86 (46.7) | 68 (37) | 9 (4.9) | 163 (88.6) | 88 (47.3) | 63 (33.9) | 12(6.5) | 163 (87.6) |
| **Gastrointestinal** | | | | | | | | |
| Diarrhea | 53 (28.8) | – | – | 53 (28.8) | 45 (14.2) | – | – | 45 (24.2) |
| Proctitis | 9 (4.9) | – | – | 9 (4.9) | 6 (3.2) | 1 (0.5) | – | 7 (3.8) |
| Rectal hemorrhage | 14 (7.6) | 2 (1.1) | – | 16 (8.7) | 10 (5.3) | 1 (0.5) | | 11 (5.9) |
| **Genitourinary** | | | | | | | | |
| Urinary frequency | 64 (35.3) | – | – | 65 (35.3) | 58 (31.2) | – | – | 58 (31.2) |
| UT obstruction | 13 (7.1) | – | – | 13 (7.1) | 11 (5.9) | 1 (0.5) | – | 12 (6.5) |
| UT pain | 20 (10.9) | – | – | 20 (10.9) | 36 (13.9) | 1 (0.5) | – | 27 (14.5) |
| Urinary urgency | 20 (10.9) | – | – | 20 (10.9) | 18 (9.7) | 1 (0.5) | – | 19 (10.2) |
| UT infection | 7 (3.8) | 2 (1.1) | | 9 (4.9) | 8 (4.3) | 2 (1.1) | | 10 (5.4) |
| **Hormonal** | | | | | | | | |
| Fatigue | 37 (20.1) | – | – | 37 (20.1) | 54 (29) | – | – | 54 (29) |
| Hot flashes | 71 (37.5) | 2 (1.1) | | 63 (38.6) | 74 (39.8) | 1 (0.5) | – | 75 (40.3) |
| ISR | 1 (0.5) | | | 1 (0.5) | 31 (16.7) | | | 31 (16.7) |

ISR = injection site reaction; UT = urinary tract.

arm and 19.9% in the degarelix arm; the difference between the arms was not significant ($\chi^2$ test, $p = 0.8$). The percentage of patients who discontinued treatment because of toxicity was 5.8% in the agonist arm and 5.6% in the degarelix arm.

A history of CVEs was reported by 10.1% of patients in the agonist arm and 11.6% in the degarelix arm. Among patients without a CVE history, an on-study CVE occurred in 6.7% of patients in the agonist arm and 5.5% in the degarelix arm. The CVE cumulative incidence rate at 2 yr was 6.4% (95% CI 2.9–11.7%) in the agonist arm and 5.6% (95% CI 2.4–10.9%) in the degarelix arm (HR 0.81, 95% CI 0.35–1.90; Supplementary Fig. 2).

Among the 41 patients with a CVE history, an on-study CVE occurred in four of 19 patients (21%) in the agonist arm and only one of 22 (4.5%) in the degarelix arm. In addi-

tion, there were two CVE-related deaths in the agonist arm. The CVE cumulative incidence rate at 2 yr was 25.7% (95% CI 7.3–49.5%) in the agonist arm and 5.0% (95% CI 0.3–21.1%) in the degarelix arm (HR 0.28, 95% CI 0.04–2.03; Fig. 2).

The median IPSS was 8 (range 0–33). Forty-two patients (22%) in the agonist arm and 46 (24%) in the degarelix arm had a baseline IPSS $\geq$ 13. There was no difference between the arms in the change in IPSS from baseline at 3 mo and 6 mo. Post hoc analyses indicated that the effects of EBRT and hormone therapy on urinary symptoms depend on IPSS at baseline (interaction test, $p < 0.001$; Fig. 3). For patients with baseline IPSS <13, the adjusted mean changes in IPSS from baseline was 4.6 (95% CI 2.0–7.2) at 3 mo and 4.2 (95% CI 1.7–6.7) at 6 mo in the agonist arm, and 4.7 (95% CI 2.1–7.3) at 3 mo and 4.0 (95% CI 1.4–6.6) at 6 mo in the degarelix arm. For patients with baseline IPSS $\geq$13, the adjusted mean change from baseline was −3.4 (95% CI −6.6 to −0.1) at 3 mo and −2.7 (95% CI −5.8 to −0.5) at 6 mo in the agonist arm, and −4.6 (95% CI −7.6 to −1.6) at 3 mo and −4.7 (95% CI −7.7 to −1.6) at 6 mo in the degarelix arm.

There was a general decline in global quality of life at 3 mo and 6 mo according to EORTC QLQ-C30 scores, with no significant difference between the treatment arms. Urinary, bowel, and sexual bother, assessed via EORTC QLQ-PR25, generally declined during the first 6 mo in comparison to baseline, with a comparable effect between the arms (Supplementary Fig. 3).

## 4. Discussion

The phase 3 EORTC 1414 trial is the only study comparing the LHRH antagonist degarelix to an LHRH agonist in patients with very high-risk localized prostate cancer treated with curative EBRT. Although the study did not complete accrual and was not analyzed as initially designed, it provides insights that merit discussion.

The trial failed to meet its modified primary endpoint and showed no superiority of degarelix over LHRH agonists in achieving a PSA nadir <0.1 ng/ml within 6 mo after EBRT. This endpoint was selected following a publication by the ICECaP Consortium that suggested that PSA $\geq$0.1 ng/ml within 6 mo after EBRT completion was a prognostic factor for poorer outcomes for patients treated with EBRT with or without ADT for localized prostate cancer [11]. Although the follow-up was not mature and long-term data are missing, the study revealed no clinically relevant difference in PFS rates at 2 yr between the agonist and degarelix arms.

Moderate to severe LUTS are common among men receiving radiotherapy with or without ADT for localized prostate cancer. The EORTC 1414 IPSS analysis confirms previous data indicating that the effects of EBRT and long-term ADT on urinary symptoms depend on the level of symptoms at baseline [14]. For patients with mild symptoms, EBRT and long-term ADT temporarily worsen urinary

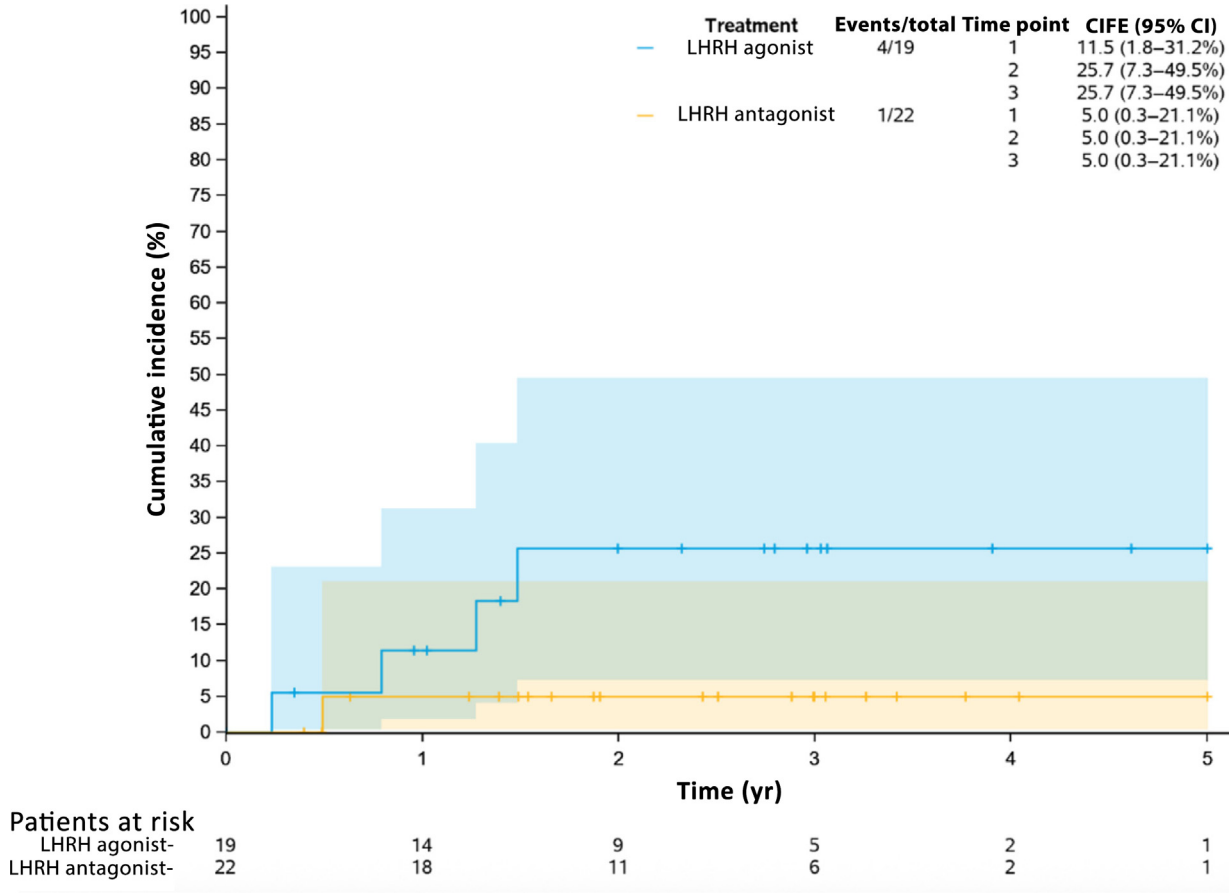


**Fig. 2 – CVE cumulative incidence events in the group of patients with a pre-existing cardiovascular condition. CI = confidence interval; CIFE = cumulative incidence function estimate; CVE = cardiovascular event; LHRH = luteinizing hormone–releasing hormone.**

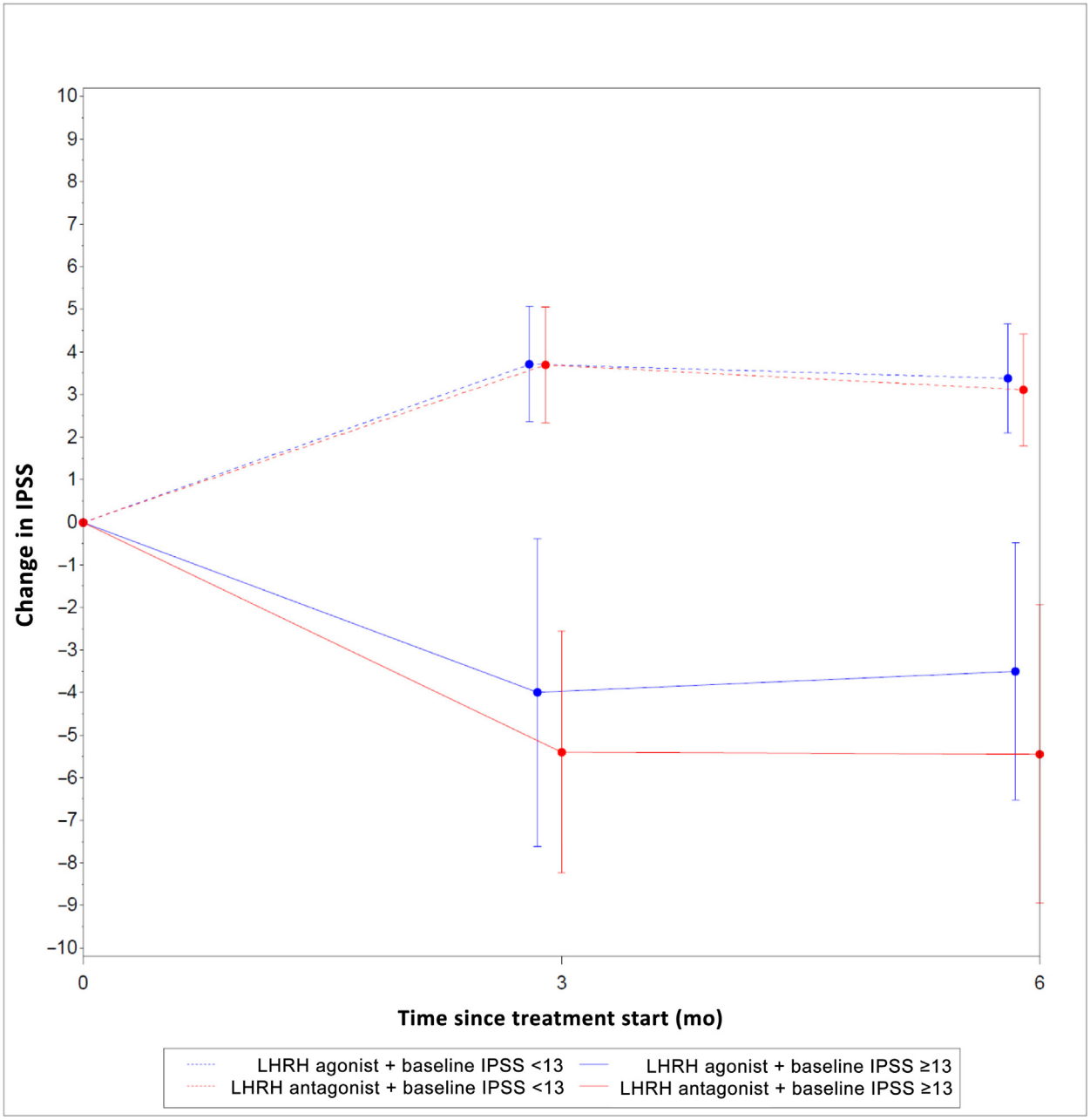


**Fig. 3 – Changes in the mean International Prostate Symptom Score (IPSS) from baseline to 3 mo and 6 mo, stratified by baseline IPSS <13 versus ≥13 points. LHRH = luteinizing hormone–releasing hormone.**

function, as shown in a study by Tomita et al [14]. By contrast, EBRT combined with long-term ADT improves urinary symptoms in patients who have severe urinary symptoms at baseline. A pooled analysis of three phase 3 trials comparing degarelix with an LHRH agonist suggests that degarelix results in significantly greater IPSS reductions than goserelin at week 12, especially for patients with baseline IPSS ≥13 [8]. For patients with IPSS ≥13 at baseline, the change in IPSS at week 12 was −2.56 (95% CI −4.34 to −0.79; $p$ = 0.005) favoring degarelix [8]. The EORTC 1414 data show a similar difference at 6 mo, with IPSS decreasing by −4.7 (95% CI −7.7 to 1.6) with degarelix versus −2.7 (95% CI −5.8 to −0.5) with an agonist. A similar trend was observed at 3 mo. However, we cannot rule out a statistical phenomenon called "regression to the mean", whereby extreme values tend to normalize over time.

The CVE rate is high in prostate cancer, but the contribution of ADT is unclear [15]. Despite a negative dedicated CVE trial, a recent meta-analysis found that LHRH antagonists cause fewer CVEs than LHRH agonists [9]. The cumulative incidence of a new CVE at 2 yr in EORTC 1414 was 6.4% in the agonist arm and 5.6% in the degarelix arm (HR 0.81, 95% CI 0.35–1.90), similar to rates in the PRONOUNCE trial [16]. According to oncology-focused trials, the reduction in cardiovascular risk with antagonists is greater for patients with a CVE history [5,7,15]. This was evident in

the trial: among 41 patients with a CVE history, four of 19 (21.1%) randomized to the agonist arm experienced a subsequent CVE, compared to one of 22 (4.5%) in the degarelix arm. There were also two CVE-related deaths in the agonist arm.

The trial has some limitations. EORTC 1414 highlights the challenges of conducting large, multinational studies in a rapidly changing clinical environment. It was launched alongside the ENZARAD (NCT02446444) and ATLAS (NCT02951052) trials, which investigated addition of an androgen receptor pathway inhibitor to ADT. Many investigators believed that this question was more important. The trial was underpowered for assessment of the difference between LHRH agonists and degarelix in terms of PFS because only 43% of the target population was enrolled. This led to a change in the primary outcome from PFS to the PSA nadir within 6 mo after EBRT, for which there was adequate statistical power for group comparisons, but this is less clinically meaningful, as the PSA nadir represents a validated prognostic factor rather than a formally accepted surrogate for comparison of ADT clinical outcomes for patients treated with EBRT and ADT for localized prostate cancer. Although an independent statistician assessed the statistical properties of the study for the new primary endpoint and the IDMC approved the change, such on-study modifications may raise questions about how interpretable and generalizable the results are, thereby rendering the analyses exploratory and primarily hypothesis-generating. Nevertheless, the findings deserve to be shared with the scientific community. Since trial initiation, new evidence for the oral LHRH antagonist relugolix has demonstrated sustained castration levels and a favorable safety profile in patients receiving curative EBRT [17]. Furthermore, consistent with our results for degarelix, relugolix was associated with a significantly lower risk of major CVEs, particularly among patients with pre-existing cardiovascular disease [15].

## 5. Conclusions

EORTC 1414 is the first prospective randomized trial comparing EBRT and long-term ADT with degarelix or an LHRH agonist. The study did not show a benefit of either approach in achieving PSA <0.1 ng/ml at 6 mo, either initially or during follow-up. However, despite a small number of events, the study results show the potential advantages of LHRH antagonists in controlling LUTS and reducing ADT-induced CVEs in patients with a history of cardiovascular disease.

***Author contributions***: Thomas Zilli 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.

*Study concept and design*: Zilli, Tombal, Böhmer, Lara, Fournier, Fortpied.
*Acquisition of data*: All authors.
*Analysis and interpretation of data*: Zilli, Tombal, Fournier, Fortpied.
*Drafting of the manuscript*: Zilli, Tombal, Fournier, Fortpied.
*Critical revision of the manuscript for important intellectual content*: All authors.
*Statistical analysis*: Fortpied.
*Obtaining funding*: Fournier, Fortpied.
*Administrative, technical, or material support:* Fournier, Fortpied.
*Supervision*: Zilli, Tombal, Böhmer, Lara, Fournier.
*Other*: None.

***Financial disclosures:*** Thomas Zilli 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: Thomas Zilli reports payments/honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Astellas, Accord, Janssen, Bayer, and Recordati. Andreas Roeder reports payments/honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Bayer, Johnson & Johnson, Pfizer, MSD, Astellas, and AstraZeneca; a data safety/advisory board role for Astellas, Bayer, AstraZeneca, and Pfizer. Stéphane Supiot reports grants from AstraZeneca and Johnson & Johnson; consulting fees from Astellas, Ipsen, Bayer, Recordati, Ferring, and Accord; and a data safety/advisory board role for Johnson & Johnson. The remaining authors have nothing to disclose.

***Funding/Support and role of the sponsor***: This study was funded by an educational grant from Ferring and was supported by Kom op tegen Kanker (Stand up to Cancer, Belgium). The funding bodies played no direct role in the study. The EORTC provided administrative, technical, and material support, and played a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; an preparation, review, and approval of the manuscript.

***Acknowledgments***: Samples used in this project were processed and stored under the management of the Integrated Biobank of Luxembourg following ISO 17025:2005 standards and International Society for Biological and Environmental Repositories best practices.

***Data sharing statement***: Data will be shared according to the EORTC data release policy (https://www.eortc.org/data-sharing/).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2025.10.009.

## References

[1] Kishan AU, Sun Y, Hartman H, et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol 2022;23:304–16.
[2] Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:1119–34.
[3] Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008;102:1531–8.
[4] Millar RP, Lu ZL, Pawson AJ, Flanagan CA, Morgan K, Maudsley SR. Gonadotropin-releasing hormone receptors. Endocr Rev 2004;25:235–75.
[5] Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 2014;65:565–73.

[6] Klotz L, Miller K, Crawford ED, et al. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. Eur Urol 2014;66:1101–8.
[7] Margel D, Peer A, Ber Y, et al. Cardiovascular morbidity in a randomized trial comparing GnRH agonist and GnRH antagonist among patients with advanced prostate cancer and preexisting cardiovascular disease. J Urol 2019;202:1199–208.
[8] Mason M, Richaud P, Bosnyak Z, Malmberg A, Neijber A. Degarelix versus goserelin plus bicalutamide in the short-term relief of lower urinary tract symptoms in prostate cancer patients: results of a pooled analysis. Low Urin Tract Symptoms 2017;9:82–8.
[9] Nelson AJ, Lopes RD, Hong H, et al. Cardiovascular effects of GnRH antagonists compared with agonists in prostate cancer: a systematic review. JACC Cardio Oncol 2023;5:613–24.
[10] Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol 2010;57:836–42.
[11] Kwak L, Ravi P, Armstrong JG, et al. Prognostic impact of prostate-specific antigen at 6 months after radiotherapy in localized prostate cancer: an individual patient data analysis of randomized trials. J Clin Oncol 2024;42:2132–8.
[12] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[13] Fayers P, Aaronson N, Bjordal K, et al. The EORTC QLQ-C30 scoring manual (3rd edition). Brussels, Belgium: European Organization for Research and Treatment of Cancer; 2001.
[14] Tomita N, Oze I, Shimizu H, et al. International Prostate Symptom Score (IPSS) change and changing factor in intensity-modulated radiotherapy combined with androgen deprivation therapy for prostate cancer. Nagoya J Med Sci 2015;77:637–46.
[15] Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020;382:2187–96.
[16] Lopes RD, Higano CS, Slovin SF, et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial. Circulation 2021;144:1295–307.
[17] Spratt DE, George DJ, Shore ND, et al. Efficacy and safety of radiotherapy plus relugolix in men with localized or advanced prostate cancer. JAMA Oncol 2024;10:594–602.