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Prostate Cancer

Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists

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Abstract

Background: Studies comparing the gonadotropin-releasing hormone antagonist, degarelix, with luteinising hormone-releasing hormone (LHRH) agonists indicate differences in outcomes.
Objective: To assess differences in efficacy and safety outcomes in a pooled analysis of trials comparing degarelix with LHRH agonists.
Design, setting, and participants: Data were pooled from five prospective, phase 3 or 3b randomised trials (n = 1925) of degarelix and leuprolide or goserelin in men requiring androgen deprivation therapy for the treatment of prostate cancer. Patients received either 3 mo (n = 467) or 12 mo (n = 1458) of treatment.
Intervention: Men were randomised to receive degarelix (n = 1266), leuprolide (n = 201), or goserelin (n = 458).
Outcome measurements and statistical analysis: Unadjusted Kaplan-Meier analyses were supported by the Cox proportional hazards model, adjusted for disease-related baseline factors, to estimate hazard ratios (HRs) of efficacy and safety outcomes. The Fisher exact test compared crude incidences of adverse events.
Results and limitations: Prostate-specific antigen (PSA) progression-free survival (PFS) was improved in the degarelix group (HR: 0.71; p = 0.017). For patients with baseline PSA levels >20 ng/ml, the HR for PSA PFS was 0.74 (p = 0.052). Overall survival (OS) was higher in the degarelix group (HR: 0.47; p = 0.023). OS was particularly improved with degarelix in patients with baseline testosterone levels >2 ng/ml (HR: 0.36; p = 0.006). In terms of disease-related adverse events, there were, overall, fewer joint-related signs and symptoms, musculoskeletal events, and urinary tract events in the degarelix group.
Conclusions: These data indicate clinical benefits with degarelix, including a significant improvement in PSA PFS and OS, as well as reduced incidence of joint, musculoskeletal, and urinary tract adverse events, compared with LHRH agonists.

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1. Introduction

Analogues of gonadotropin-releasing hormone (GnRH), such as luteinising hormone-releasing hormone (LHRH) agonists and GnRH antagonists, suppress testosterone to below castrate levels. The pivotal phase 3 study CS21 compared androgen deprivation with the GnRH antagonist degarelix and the LHRH agonist leuprolide. Treatment with degarelix was noninferior for the proportion of patients achieving castrate testosterone levels over 1 yr of treatment [1] and provided significantly longer prostate-specific antigen (PSA) progression-free survival (PFS) [2]. Further studies showed a benefit with degarelix compared to goserelin plus antiandrogen in relief from lower urinary tract symptoms (LUTS) [3–5]. Both International Prostate Symptom Score (IPSS) improvement and prostate volume reduction were greater with degarelix.

Androgen suppression commonly causes hot flushes, weight gain, and fatigue. In comparative phase 3 trials, these adverse events (AEs) were similar for degarelix and LHRH agonists. Some differences also emerged: The frequency of injection-site reactions was higher with degarelix [1,6] and incidence of disease-related AEs such as arthralgia and urinary tract infections (UTIs) were higher with leuprolide [1].

The purpose of the present analysis was to assess efficacy and safety outcomes from a pooled analysis of five randomised phase 3/3b trials comparing degarelix with LHRH agonists as androgen deprivation therapy (ADT) in men with prostate cancer (PCa).

2. Patients and methods

Individual patient data were pooled from five prospective, phase 3 or 3b randomised trials ($n = 1925$) comparing degarelix with a LHRH agonist [1,3–6]. Patients received 1 yr ($n = 1458$) or 3 mo ($n = 467$) of degarelix or LHRH agonist treatment (Table 1). Antiandrogen use in the LHRH agonist arm was at the investigator's discretion in 12-mo trials and mandated in the 3-mo trials. The full analysis set ($n = 1920$) comprised patients in the intent-to-treat population with at least one postbaseline measurement. The initial degarelix dose was 240 mg in all trials. Maintenance doses were 80 mg except in CS21, which compared maintenance doses of 80 mg and 160 mg, and CS35, which used a maintenance regimen of 480 mg every 3 mo. Clinical trials were performed in accordance with the Declaration of Helsinki and good clinical practice guidelines. The respective study protocols were approved by independent ethics committees and institutional review boards. All patients provided written informed consent.

PSA PFS was defined as death or PSA recurrence (two consecutive PSA increases of ≥50% vs nadir and ≥5 ng/ml on two consecutive measurements at least 2 wk apart with the end point recorded on the date of the second measurement according to CS21 protocol criteria).

Table 1 – Randomised comparative phase 3 trials of degarelix and luteinising hormone-releasing hormone agonists included in the pooled analysis (safety analysis set)

Authors/trial	Study arms (dose*, mg)	Patients, no.	Follow-up, mo	Main PCa inclusion criteria	Primary end point
Klotz et al. [1]/CS21	Degarelix (240/80) Degarelix (240/160) Leuprolide (7.5)	207 202 201	12	• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy • Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intent • PSA level at screening >2 ng/ml	• Probability of testosterone ≤0.5 ng/ml from days 28–364
Anderson et al. [4]/CS28	Degarelix (240/80) Goserelin (3.6)	27 13	3	• PSA level at screening >10 ng/ml • TNM staging at baseline: T3/4, any N, any M • IPSS ≥12	• Change from baseline in total IPSS at week 12 using the last observation carried forward approach
Mason et al. [5]/CS30	Degarelix (240/80) Goserelin (3.6)	181 64	3	• Planned for radical radiotherapy treatment and in whom neoadjuvant is indicated • TNM stage: T2 (b or c)/T3/T4, N0, M0; or Gleason score ≥7 or PSA level ≥10 ng/ml	• Mean percentage reduction in prostate volume at 12 wk as compared to baseline
Axcrona et al. [3]/CS31	Degarelix (240/80) Goserelin (3.6)	84 98	3	• TNM stage: any T, any N, any M • PSA level at screening >2 ng/ml • Prostate >30 ml	• Mean percentage reduction in prostate volume measured with TRUS at 12 wk compared to baseline
Shore et al. [6]/CS35	Degarelix (240/480) Goserelin (3.6/10.8)	565 283	12	• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy • Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intent • PSA level at screening >2 ng/ml	• Cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from days 28–364 with degarelix • Difference in cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from days 3–364 between degarelix and goserelin

PCa = prostate cancer; PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; TRUS = transrectal ultrasound.
* Values indicate initial dose and, if relevant, maintenance dose monthly or every 3 mo.

Time-to event was the time from first dose to first event, or to loss of follow-up due to any cause, whichever came first. In the latter case, data were right censored. Events, or loss to follow-up, occurring beyond the comparative phase of the respective trials were right censored at day 364 and day 83 for the 12- and 3-mo trials, respectively. The time-to event for PSA PFS and overall survival (OS) were analysed using Kaplan-Meier methods and *p* values reported from the log-rank test. The number of events for all Kaplan-Meier analyses are shown in Supplemental Table 1. To address the influence of and produce balanced estimates with respect to disease-related factors (age, disease stage, log PSA, and testosterone) on the time-to event end points, a multivariate Cox proportional hazards model was used. Due to a lack of geographic consistency and absence of centralised review of Gleason scores, this factor was not included in the analyses. Adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and *p* values based on the Wald test are reported. An additional study-by-treatment interaction effect, describing the difference between the 12-mo and 3-mo trials, was significant for musculoskeletal and urinary tract events and was included in the analysis of these end points, together with study as main effect. The Medical Dictionary for Regulatory Activities (MedDRA) v.15.0 preferred terms included in these disease-related end points are listed in Supplemental Table 2.

Mean changes from baseline in serum alkaline phosphatase (S-ALP) throughout the course of the treatment period were analysed based on a longitudinal repeated-measures analysis of covariance model and significance of difference between the two treatments was tested using a *t* test.

Comparisons of crude incidence of AEs were performed using the two-sided Fisher test. AE data were coded according to MedDRA and reported by high-level term and preferred term. Patients with cardiovascular disease at baseline were defined as those having any medical history of myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events (arterial), or other ischaemic heart disease as defined by standardised MedDRA queries.

For all tests, a *p* value <0.05 was considered significant and no adjustments for multiple comparisons were made. Data analysis was performed using SAS v.9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

Data from 1925 patients were analysed (safety analysis set); 1266 patients received degarelix and 659 received a LHRH agonist (goserelin, $n = 458$; leuprolide, $n = 201$). The full analysis set (efficacy analyses) consisted of 1920 patients, 1263 of whom received degarelix, and 456 and 201 of whom received the LHRH agonists goserelin and leuprolide, respectively. Median follow-up was 364 d (interquartile range: 116–364 d) and was equivalent for the two treatment groups. Patient demographics and baseline characteristics were similar between treatment groups (Table 2).

Table 2 – Patient demographics and baseline characteristics (full analysis set)

	Degarelix ($n = 1263$)	LHRH agonist ($n = 657$)
Age, yr, median (range)	72 (46–94)	72 (51–98)
Age >70 yr, no. (%)	732 (58)	389 (59)
Geographic region, no. (%)		
Americas	380 (30)	188 (29)
Western Europe	269 (21)	160 (24)
Eastern Europe	614 (49)	309 (47)
Testosterone level, ng/ml, median (IQR)	4.2 (3.1–5.4)	4.3 (3.3–5.4)
Testosterone >2 ng/ml, no. (%)	1176 (93)	628 (96)
PSA level, ng/ml, median (IQR)	17.3 (8.6–53.7)	16.7 (7.7–51.1)
PSA subgroups, no. (%)		
0–10	391 (31)	224 (34)
10–20	283 (23)	140 (21)
20–50	250 (20)	124 (19)
>50	328 (26)	165 (25)
PCa stage, no. (%)		
Localised	432 (34)	226 (34)
Locally advanced	375 (30)	170 (26)
Metastatic	282 (22)	153 (23)
Not classified	174 (14)	108 (16)
Gleason score, no. (%)		
2–4	91 (7)	41 (6)
5–6	381 (30)	179 (27)
7–10	784 (62)	436 (66)
Antiandrogen treatment		
Yes	20 (2)	242 (37)
No	1243 (98)	415 (63)

IQR = interquartile range; LHRH = luteinising hormone-releasing hormone; PCa = prostate cancer; PSA = prostate-specific antigen.

3.1. *Efficacy outcomes*

Kaplan-Meier estimates of time to PSA PFS for all patients are illustrated in Figure 1a (log-rank test $p = 0.042$). PSA PFS events occurred predominantly in patients with high baseline PSA levels; 18.2% of degarelix patients and 24.9% of LHRH patients with baseline PSA values >20 ng/ml met the PSA PFS criteria after up to 1 yr of treatment compared with only 2% and 3% of degarelix and LHRH agonist patients with PSA value ≤20 ng/ml at baseline, respectively. Figure 1b illustrates Kaplan-Meier estimates of time to PSA PFS for patients with baseline PSA values >20 ng/ml (log-rank test $p = 0.022$). All disease factors were significant when included in the Cox proportional hazards model. For all patients, the adjusted HR for degarelix versus LHRH agonist was 0.71 ($p = 0.017$) (Table 3) and for patients with baseline PSA levels >20 ng/ml, the HR was 0.74 (95% CI, 0.55–1.00; $p = 0.052$).

There were 18 deaths (1%) in the degarelix group and 19 deaths (3%) in the LHRH agonist group. Four patients died of PCa (degarelix, $n = 3$; LHRH agonists, $n = 1$). All causes of death are listed in Supplemental Table 3. Kaplan-Meier estimates for OS are depicted in Figure 2 (log-rank test $p = 0.031$). When adjusted for confounding baseline factors, the HR for risk of death with degarelix was 0.47 ($p = 0.023$) (Table 3). The outcome of survival depended on testosterone level. Disease stage, age and baseline PSA did not affect OS.

The HRs for OS and PSA PFS for the 12-mo trials CS21 and CS35 are shown in Figure 3. The Cox proportional model

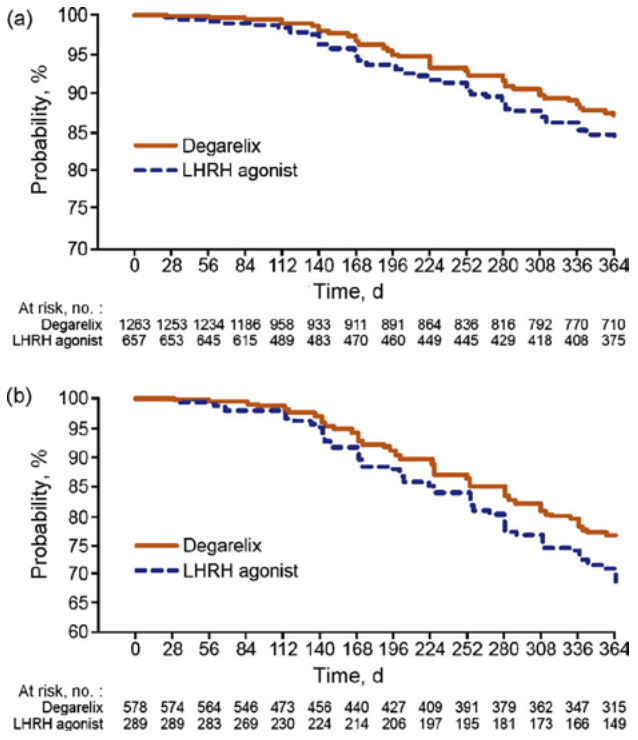

Fig. 1 – Probability of prostate-specific antigen (PSA) progression-free survival in (a) all patients and (b) those with baseline PSA >20 ng/ml. LHRH = luteinising hormone-releasing hormone.

behind this illustrative analysis took into account study and study-by-treatment interaction terms. The 3-mo trials are not included, due to a lack of events (two deaths and six PSA PFS events, all in the LHRH agonist group).

For OS, interaction effects between both testosterone level and treatment and age and treatment were significant when included in the Cox proportional hazards model. For patients with baseline testosterone values >2 ng/ml (94%), the HR was 0.36 (95% CI, 0.17–0.75; $p = 0.006$) and in patients aged >70 yr (58%), the HR was 0.29 (95% CI, 0.12–0.70; $p = 0.006$) for degarelix versus LHRH agonist. Patients with underlying cardiovascular disease at baseline (29.6%) showed a nonsignificant trend for a lower risk of death with degarelix versus LHRH agonists (HR: 0.40; 95% CI, 0.16–1.01; $p = 0.051$) when adjusted for confounding baseline factors.

In patients with metastatic disease, S-ALP was suppressed to a greater extent throughout the 1-yr treatment period by degarelix ($p = 0.037$). The mean adjusted change from baseline at day 364 for degarelix was −90.3 IU/l versus −31.5 IU/l for LHRH agonist-treated patients (Supplemental Fig. 1).

3.2. *Safety outcomes*

Treatment-emergent AEs were reported in 74% and 68% of patients receiving degarelix or LHRH agonist, respectively (Table 4). Hot flush was reported by 386 (30%) and 171 (26%) of degarelix and LHRH agonist-treated patients, respectively.

Table 3 – Multivariate analysis for individual end points in overall population

	PSA PFS	Overall survival	Joint-related signs and symptoms	Urinary tract event[†]	Musculoskeletal event[†]
Degarelix vs LHRH agonist	**0.71** (0.54–0.94; 0.017)	**0.47** (0.25–0.90; 0.023)	**0.64** (0.42–0.98; 0.041)	**0.50** (0.39–0.66; <0.001) (12 mo) **1.64** (0.90–3.00; 0.106) (3 mo)	**0.55** (0.40–0.76; <0.001) (12 mo) **2.04** (0.91–4.55; 0.082) (3 mo)
Testosterone (ref: 1 ng/ml)	**0.90** (0.83–0.97; 0.005)	**0.63** (0.49–0.79; <0.001)	**1.00** (0.89–1.12; 0.979)	**0.89** (0.83–0.96; 0.001)	**0.95** (0.87–1.03; 0.173)
Log PSA (ref: 1 log ng/ml)	**1.42** (1.32–1.54; <0.001)	**1.12** (0.93–1.35; 0.232)	**0.95** (0.82–1.10; 0.499)	**1.05** (0.97–1.14; 0.202)	**1.02** (0.93–1.12; 0.725)
Disease stage (ref: localized)					
Locally advanced	**1.73** (0.97–3.09; 0.065)	**0.58** (0.17–1.97; 0.385)	**0.86** (0.47–1.60; 0.641)	**0.72** (0.52–1.01; 0.059)	**0.70** (0.46–1.08; 0.107)
Metastatic	**5.05** (2.92–8.74; <0.001)	**2.37** (0.90–6.21; 0.080)	**1.57** (0.84–2.92; 0.154)	**0.93** (0.64–1.35; 0.685)	**1.61** (1.06–2.46; 0.027)
Not classifiable	**1.51** (0.74–3.06; 0.256)	**1.60** (0.58–4.43; 0.366)	**1.31** (0.70–2.44; 0.403)	**1.49** (1.07–2.08; 0.018)	**1.29** (0.83–2.00; 0.257)
Age (ref: 1 yr)	**0.96** (0.94–0.97; <0.001)	**1.01** (0.98–1.06; 0.490)	**1.02** (1.00–1.05; 0.104)	**1.01** (0.99–1.02; 0.312)	**1.01** (0.99–1.03; 0.418)

PFS = progression-free survival; PSA = prostate-specific antigen.
Data given as estimated hazard ratio (95% confidence interval; *p* value) after multivariate analysis using the Cox proportional hazards model.
[†] Urinary tract events and musculoskeletal events demonstrated significant heterogeneity between the 12-mo and 3-mo trials. Thus the interaction term describing this was included in the Cox proportional hazards model and estimated hazard ratios within each group of trials reported.

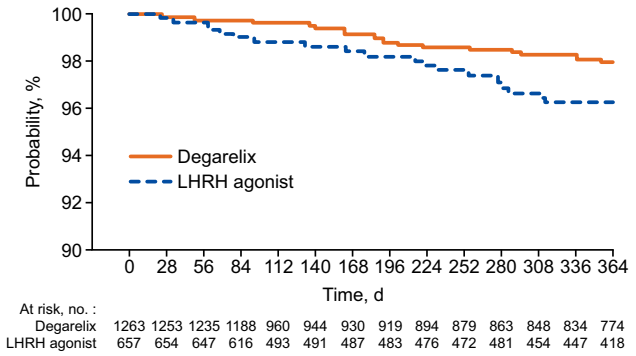

Fig. 2 – Probability of overall survival. LHRH = luteinising hormone-releasing hormone.

Injection-site reactions, including pain, erythema, swelling, and nodules, were more frequent in the degarelix group. Back pain and UTI were more frequent in the LHRH agonist group (Table 4).

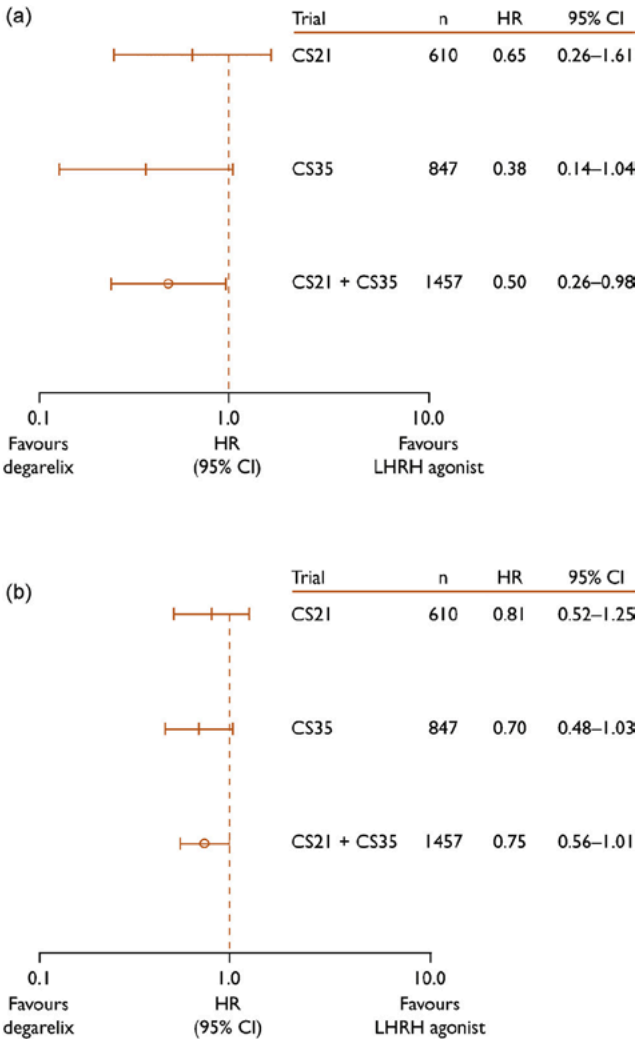

Fig. 3 – Forest plot detailing homogeneity in the hazard ratios for events in trials CS21 and CS35: (a) overall survival; (b) prostate-specific antigen progression-free survival. CI = confidence interval; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone.

Table 4 – Treatment-emergent adverse events (>5% in either group)

Adverse event	Degarelix, no. (%)	LHRH agonist, no. (%)	*p* value*
Safety analysis set	1266 (100)	659 (100)	–
Any adverse event	942 (74)	445 (68)	0.002
Hot flush	386 (30)	171 (26)	0.039
Injection-site reactions			
Pain	380 (30)	6 (<1)	<0.001
Erythema	257 (20)	0 (0)	–
Swelling	76 (6)	0 (0)	–
Nodule	73 (6)	0 (0)	–
Fatigue	59 (5)	35 (5)	0.578
Back pain	50 (4)	41 (6)	0.031
Urinary tract infection	43 (3)	37 (6)	0.023
Arthralgia	45 (4)	34 (5)	0.115

LHRH = luteinising hormone-releasing hormone.
* Two-sided Fisher exact test.

Joint-related signs and symptoms (of which the majority of events were arthralgia) were less frequent with degarelix compared with LHRH agonist-treated patients (HR: 0.64; $p = 0.041$) (Table 3). Fewer patients in the degarelix group experienced a fracture (<1% vs 2% for the LHRH agonist group), although this did not reach statistical significance (HR: 0.42; 95% CI, 0.16-1.05; $p = 0.065$); with a further differentiation for patients with baseline testosterone levels >2 ng/ml, the HR was 0.32 (95% CI, 0.12–0.89; $p = 0.028$).

Crude incidence of musculoskeletal events was 8% versus 12% for degarelix and LHRH agonist-treated patients, respectively. Overall, there were fewer events with degarelix treatment (log-rank test $p = 0.007$) (Fig. 4a). The Cox proportional hazards model accounted for a significant study-by-treatment interaction ($p = 0.003$) between the 12- and 3-mo studies. Adjusted HRs were 0.55 (95% CI, 0.40–0.76; $p < 0.001$) and 2.04 (95% CI, 0.91–4.55; $p = 0.082$), for the 12- and 3-mo studies, respectively. The only baseline factor that had an impact on musculoskeletal events was disease stage (Table 3).

Crude incidence of a urinary tract event was 12% versus 18%. Figure 4b illustrates the Kaplan-Meier estimate of time to urinary tract event (log-rank test $p < 0.001$). Again, the 12-mo studies were significantly different to the 3-mo studies (interaction term $p < 0.001$). Adjusted HRs were 0.50 ($p < 0.001$) and 1.64 ($p = 0.11$) for the 12- and 3-mo studies, respectively (Table 3). Urinary tract events were also related to PCa stage and baseline testosterone level. Infections comprised 30% of urinary tract events; the adjusted HR for UTI was 0.58 (95% CI, 0.39–0.84; $p = 0.004$).

4. Discussion

Analysis of this large, pooled patient population demonstrated important differences in efficacy (PSA PFS and OS) and disease-related outcomes (musculoskeletal and urinary tract events) when treatment with degarelix was compared to LHRH agonists. A Cox proportional hazards model adjusting for the potential influence of patient characteristics and baseline disease traits on treatment outcomes and

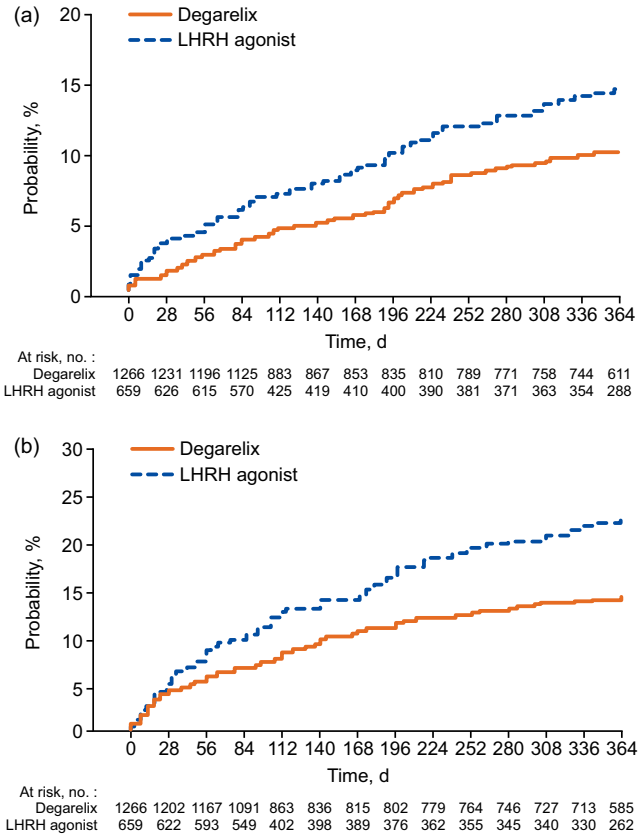

Fig. 4 – Probability of experiencing (a) a musculoskeletal event or (b) renal or urinary tract-related adverse event. LHRH = luteinising hormone-releasing hormone.

to account for potential differences in outcomes between studies confirmed the robustness of the data.

Effective PSA control is associated with improved OS [7,8]. PSA PFS was dependent upon baseline PSA level (most patients experiencing progression had baseline PSA levels >20 ng/ml). Kaplan-Meier analysis, which is unadjusted, demonstrated significantly better PSA PFS in degarelix patients with baseline PSA levels >20 ng/ml. This agrees with phase 3 trial data comparing degarelix with leuprolide, which indicated significantly better PSA PFS in this subgroup with degarelix treatment (log-rank $p = 0.01$) [2,9]. After adjusting for baseline factors using the Cox proportional hazards model, the HR for PSA PFS was 0.74 ($p = 0.052$).

Patients in the degarelix group had a lower risk for death after adjusting for confounding baseline factors. The difference in OS was not driven by PCa deaths, as only four patients died as a result of disease progression during the year of study. Recent data suggest that degarelix is associated with a lower incidence of cardiovascular events in men with preexisting cardiovascular disease [10]. This is a plausible explanation for the survival difference seen in this pooled analysis. Overall, 51% of the 37 deaths occurred in the subgroup of 29% of patients with baseline cardiovascular disease. This likely explains the greater benefit in OS for patients aged >70 yr, who are at an increased risk for cardiovascular disease.

In advanced PCa, skeletal metastases are common and associated with significant morbidity, frequently manifesting as bone pain, pathologic fractures, or spinal cord compression [11]. Furthermore, skeletal fracture is an independent negative predictor of OS in patients receiving ADT [12], and elevated S-ALP levels have been associated with progression of skeletal metastases and reduced survival times [13–15]. The current results demonstrate significantly greater S-ALP suppression in the degarelix group, suggesting better control of S-ALP and, potentially, prolonged suppression of skeletal metastases. Also, the OS benefit and lower fracture incidence in men with baseline testosterone levels >2 ng/ml treated with degarelix versus LHRH agonists are in line with these reports.

Obstructive uropathy is a common problem in locally advanced and metastatic prostate cancer, frequently leading to clinical manifestations including persistent infections [16]. In this analysis, patients receiving degarelix experienced significantly fewer urinary tract events and a longer time to first UTI than those receiving LHRH agonists. In patients with local disease requiring rapid symptom relief, degarelix was either superior or noninferior to goserelin plus bicalutamide in terms of prostate volume reduction and provided greater relief of moderate or severe LUTS [3–5]. LUTS relief may occur as a direct result of a reduction in prostate volume and via mechanisms linked to the blockade of extrapituitary GnRH receptors by degarelix [3]. Importantly, improvement in urinary symptoms is associated with increased quality of life for patients with PCa receiving ADT [3,5].

The differences in disease-related outcomes in patients with advanced disease may be explained by the distinct mode of action of degarelix compared with LHRH agonists. In contrast to LHRH agonists, degarelix causes rapid and sustained testosterone suppression [1,17,18]. Microsurges in testosterone, which may occur on agonist re-administration, could potentially adversely affect PFS [19,20]. Furthermore, a number of extrapituitary tissues, including PCa cells, express GnRH receptors on their surface [21–24], although a functional role and potential modulation of downstream effects by degarelix or LHRH agonists is undetermined. Degarelix does, however, provide improved follicle-stimulating hormone (FSH) suppression compared with LHRH agonists [1,25]. Suppression of FSH is potentially important, considering its possible role in tumour growth [26,27], bone resorption [28], and regulation of adipocytes and obesity [29]. The clinical relevance of more robust FSH suppression with degarelix has not been fully elucidated.

Despite including trials from different regions, with different inclusion criteria and study lengths, there were few interaction effects between studies and treatment groups. The outcomes of OS, PSA PFS, joint-related signs and symptoms, and UTIs were not affected. There was a significant study-by-treatment interaction effect for musculoskeletal and urinary tract events. That is, there was a significantly lower incidence for degarelix versus LHRH agonists for the 12-mo trials, while the 3-mo trials indicated

no significant difference between treatment groups. These differences could be due to the required use of an antiandrogen in the LHRH agonist arm or insufficient safety events related to a lower baseline disease burden in the patients recruited to the 3-mo trials.

Limitations of this retrospective analysis are that it was a pooled analysis of five prospective randomised trials, rather than a single randomised trial. These trials had survival as a safety end point rather than as a primary end point. The 1-yr follow-up and corresponding low mortality rate limit the strength of any conclusion about long-term outcomes.

5. Conclusions

In this analysis of 1925 patients, adjusted for the influence of confounding baseline factors, improved disease control was seen with degarelix versus LHRH agonists in patients with advanced disease.

The data confirm results from previous studies. In this pooled analysis of five prospective randomised trials, improved PSA PFS, longer OS (likely due to a decreased risk of cardiovascular disease), and decreased joint, musculoskeletal, and urinary tract events occurred with degarelix compared with LHRH agonists.

Author contributions: Laurence Klotz 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: Klotz, Miller, Crawford, Shore, Tombal, Karup, Malmberg, Persson.
Acquisition of data: Klotz, Miller, Crawford, Shore, Tombal.
Analysis and interpretation of data: Klotz, Miller, Crawford, Shore, Tombal, Karup, Malmberg, Persson.
Drafting of the manuscript: Klotz, Malmberg, Persson.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2013.12.063.

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