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# 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

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**Abstract**

***Background:*** Recent data suggest prostate-specific antigen (PSA) progression may predict overall survival in prostate cancer patients.
***Objective:*** To compare the activity of degarelix and leuprolide regarding PSA recurrence-free survival.
***Design, setting, and participants:*** Phase 3, 1-yr, multicentre, randomised, open-label trial comparing the efficacy and safety of degarelix at 240 mg for 1 mo, and then 80 mg monthly (240/80 mg); degarelix at 240 mg for 1 mo, and then 160 mg monthly; and leuprolide at 7.5 mg/mo. Overall, 610 patients with histologically confirmed prostate cancer (all stages), for whom androgen deprivation therapy was indicated, were included. The primary end point of this trial has been reported previously; the protocolled and exploratory subgroup analyses reported in this paper focus on degarelix at 240/80 mg (dose approved by the US Food and Drug Administration and the European Medicine Evaluation Association for the treatment of patients with hormone-naive advanced prostate cancer).
***Measurements:*** PSA progression-free survival (two consecutive increases in PSA of 50% compared with nadir and $\geq$5 ng/ml on two consecutive measurements at least 2 wk apart or death) and change in PSA were reviewed. Effects of baseline disease stage (localised, locally advanced, and metastatic) and PSA level ($<$10, 10–20, $>$20–50, and $>$50 ng/ml) were analysed.

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***Results and limitations:*** Patients receiving degarelix showed a significantly lower risk of PSA progression or death compared with leuprolide ( $p = 0.05$). PSA recurrences occurred mainly in patients with advanced disease and exclusively in those with baseline PSA >20 ng/ml. Patients with PSA >20 ng/ml had a significantly longer time to PSA recurrence with degarelix ( $p = 0.04$). The relatively low number of patients in each subgroup is a limitation of this study.

***Conclusions:*** These results generate the hypothesis that degarelix at 240/80 mg offers improved PSA control compared with leuprolide. PSA recurrences occurred almost exclusively in patients with metastatic prostate cancer or high baseline PSA during this 1-yr study. Further studies are warranted to confirm these findings.



## 1. Introduction

Gonadotrophin-releasing hormone (GnRH) agonists are the mainstay of androgen deprivation therapy for prostate cancer. These agents initially overstimulate GnRH receptors, and eventually, this results in suppression of luteinising hormone (LH) release through desensitisation of the pituitary–gonadal axis. This mechanism of action results in an initial testosterone surge, which in patients with advanced disease can stimulate tumour growth and exacerbate clinical symptoms (*clinical flare*) [1]. Treatment with GnRH agonists can also result in testosterone microsurges on repeat injections [2]. With chronic administration, testosterone release is suppressed and castrate levels (≤0.5 ng/ml) are achieved in 90–100% of patients after 7–21 d [3]. GnRH blockers (antagonists) are a new class of hormonal therapy that immediately block GnRH receptors, resulting in fast testosterone suppression without the surge, clinical flare, or microsurges associated with GnRH agonists [4,5].

Prostate-specific antigen (PSA) is a commonly used marker in prostate cancer screening. It can monitor response to treatment, disease recurrence, and potentially provide evidence of progression [6,7]. Absolute PSA level is also a marker of disease stage and extent of disease in prostate cancer patients. PSA control is associated with improved overall survival [8–10] and routinely used to monitor patients under therapy and assess response in most clinical settings. A recent phase 3 trial (CS21) demonstrated that degarelix, a new GnRH blocker, was associated with significantly faster LH, follicle-stimulating hormone (FSH), testosterone, and PSA suppression, and it was as effective as leuprolide in suppressing testosterone to castrate levels in prostate cancer patients over the 12-mo study period [11]. In this paper, we report exploratory subgroup analyses of PSA data from the CS21 trial.

## 2. Methods

### 2.1. Study design and patients

The methodology and results for this study have been reported previously [11]. Briefly, CS21 was a phase 3, multicentre, randomised, open-label trial powered to demonstrate the noninferiority of degarelix versus leuprolide for the primary end point (probability of patients having testosterone ≤0.5 ng/ml at each monthly measurement for 1 yr). Patients were randomised either to a degarelix starting dose of 240 mg for 1 mo and thereafter monthly doses of 80 mg (240/80 mg) or 160 mg (240/160 mg) or to leuprolide at 7.5 mg/mo. Concomitant antiandrogen could be given as flare protection to patients in the leuprolide group at the discretion of the investigator. Patients with histologically confirmed prostate cancer (all stages), for whom androgen deprivation therapy was indicated, were eligible (including patients with rising PSA after prostatectomy/radiotherapy). Patients were also required to have testosterone >1.5 ng/ml, an Eastern Cooperative Oncology Group performance status ≤2, and PSA ≥2 ng/ml.

This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Independent ethics committees and institutional review boards were utilised for participating sites.

### 2.2. Prostate-specific antigen analyses

Blood samples for PSA analyses were taken at screening and before dosing (day 0), and at days 1, 3, 7 (±2 d), and 14 (±2 d) after the initial dose. Subsequent blood samples were taken on day 28 (±2 d), then once every 28 d (±7 d) before dosing and at final study visit. PSA analyses were performed at a central laboratory by Esoterix Inc using a validated immunoassay. PSA recurrence (a secondary end point) was defined as two consecutive increases in PSA of 50% compared with 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. Analyses of PSA recurrence over time and percentage change in PSA from baseline to 14–28 d were preplanned and included in the CS21 statistical analysis plan; the remaining analyses were of an exploratory post hoc nature. PSA progression-free survival was analysed using the Kaplan-Meier method, and *time to event* was defined as the number of days from first dosing to the first of PSA recurrence or death. Overall survival was analysed using similar methodology. PSA recurrences were analysed by baseline disease stage (localised, locally advanced, metastatic) and PSA level (<10, >10–20, >20–50, and >50 ng/ml). Median percentage change in PSA level from baseline was also analysed by baseline disease stage. Statistical comparisons were performed using a Cox proportional hazards analysis adjusted for baseline disease stage and PSA level, and the log-rank test (unadjusted analysis).

These exploratory subgroup analyses focus on the comparison of leuprolide 7.5 mg/mo with degarelix 240/80 mg, in line with recent approvals of this dose for the treatment of advanced prostate cancer by the US Food and Drug Administration and the European Medicine Evaluation Association.

**Table 1 – Baseline characteristics (intent-to-treat [ITT] population)**

| | Degarelix 240/80 mg | Degarelix 240/160 mg | Leuprolide 7.5 mg/mo |
|---|---|---|---|
| ITT analysis set | 207 | 202 | 201 |
| Median age, yr (range) | 72 (51–89) | 72 (50–88) | 74 (52–98) |
| Median testosterone, ng/ml (P25–P75) | 4.11 (3.05–5.32) | 3.78 (2.86–5.05) | 3.84 (2.91–5.01) |
| Median PSA, ng/ml (P25–P75) | 19.8 (9.4–46) | 19.9 (8.2–68) | 17.4 (8.4–56) |
| Stage of disease, *n* (%) | | | |
| Localised[a] | 69 (33) | 59 (29) | 63 (31) |
| Locally advanced[b] | 64 (31) | 62 (31) | 52 (26) |
| Metastatic[c] | 37 (18) | 41 (20) | 47 (23) |
| Not classifiable[d] | 37 (18) | 40 (20) | 39 (19) |
| Gleason score, *n* (%) | | | |
| 2–4 | 20 (10) | 21 (11) | 24 (12) |
| 5–6 | 68 (33) | 67 (34) | 63 (32) |
| 7 | 63 (30) | 56 (28) | 62 (31) |
| 8–10 | 56 (27) | 56 (28) | 51 (26) |
| PSA subgroup, *n* (%) | | | |
| <10 ng/ml | 55 (27) | 65 (32) | 64 (32) |
| 10–20 ng/ml | 52 (25) | 36 (18) | 44 (22) |
| >20–50 ng/ml | 52 (25) | 38 (19) | 38 (19) |
| >50 ng/ml | 48 (23) | 63 (31) | 55 (27) |

240/80 mg = 240 mg for 1 mo, and then 80 mg monthly; 240/160 mg = 240 mg for 1 mo, and then 160 mg monthly; PSA = prostate-specific antigen.
[a] Localised: T 1/2, NX or N0, and M0; four patients (6.3%) received antiandrogen flare protection.
[b] Locally advanced: T3/4; Nx or N0, and M0; or N1 and M; six patients (11.5%) received antiandrogen flare protection.
[c] Metastatic: Nine patients (19.1%) received antiandrogen flare protection.
[d] Includes those with rising PSA after radical prostatectomy or radiotherapy; three patients (7.7%) received antiandrogen flare protection.

**Table 2 – Overall incidence and probability of prostate-specific antigen (PSA) recurrence or death (intent-to-treat population)**

| | Degarelix 240/80 mg (*n* = 207) | Degarelix 240/160 mg (*n* = 202) | Leuprolide 7.5 mg/mo (*n* = 201) |
|---|---|---|---|
| Incidence of PSA recurrence, *n* (%) | 16 (7.7) | 26 (12.9) | 26 (12.9) |
| Probability of PSA recurrence,[a] % (95% CI) | 8.9 (5.5–14.1) | 14.2 (9.9–20.2) | 14.1 (9.8–20.1) |
| Incidence of death, *n* (%) | 5 (2) | 5 (2) | 9 (4) |
| Probability of death,[a] % (95% CI) | 2.6 (1.1–6.2) | 2.9 (1.2–6.8) | 4.9 (2.6–9.3) |

240/80 mg = 240 mg for 1 mo, and then 80 mg monthly; 240/160 mg = 240 mg for 1 mo, and then 160 mg monthly; CI = confidence interval.
[a] Probability of experiencing PSA recurrence or death by day 364 (estimated using the Kaplan-Meier method).

## 3. Results

### 3.1. Patients

Overall, 610 patients were treated, and baseline characteristics were well balanced between groups (Table 1). Approximately half of these patients had advanced disease (49.7%) or PSA >20 ng/ml (48.2%) at baseline. Median age was 73 yr, median testosterone was 3.93 ng/ml, and median PSA was 19.0 ng/ml. Overall, 22 patients (10.9%) in the leuprolide group received concomitant antiandrogen flare protection. Of these patients, 9 patients had metastatic disease and 14 had PSA >20 ng/ml at baseline.

### 3.2. Overall analysis of prostate-specific antigen recurrences, prostate-specific antigen progression-free survival, and overall survival

Table 2 shows the incidences of PSA recurrence and death. PSA recurrence occurred more frequently in patients receiving leuprolide (12.9%) compared with degarelix 240/80 mg (7.7%). The probability of completing the study without experiencing PSA recurrence by day 364 was 91.1% (95% confidence interval [CI], 85.9–94.5) for degarelix and 85.9% (95% CI, 79.9–90.2) for leuprolide. The probability of completing the study without dying by day 364 was 97.4% (95% CI, 93.8–98.9) for degarelix and 95.1% (95% CI, 90.7–97.4) for leuprolide. Patients receiving degarelix had a statistically lower risk of PSA recurrence or death compared with leuprolide ($p = 0.05$; log-rank). Adjusting for baseline disease stage and PSA resulted in a hazard ratio (HR) of 0.664 (95% CI, 0.385–1.146; Fig. 1). Overall survival is shown in Fig. 2.

### 3.3. Prostate-specific antigen recurrence by baseline disease stage and prostate-specific antigen levels

PSA recurrence occurred more frequently in patients with advanced disease in both treatment groups (Fig. 3a). In patients with metastatic disease, 21.6% of those in the degarelix 240/80 mg group and 36.2% of those in the leuprolide group experienced PSA recurrence ($p = 0.156$). Time to PSA recurrence in patients with metastatic disease is shown in Fig. 4a ($p = 0.149$). A similar

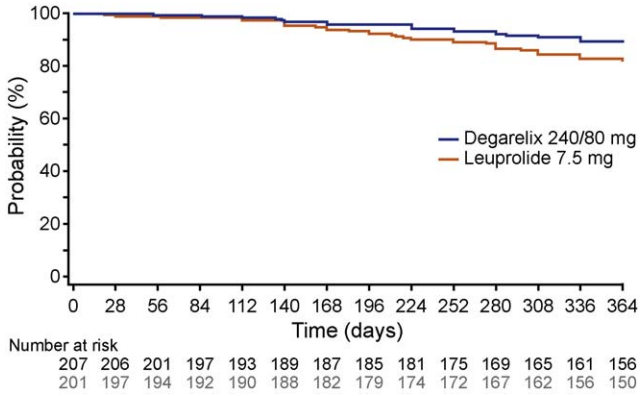


**Fig. 1 – Probability of freedom from prostate-specific antigen recurrence or death (intent-to-treat population).**

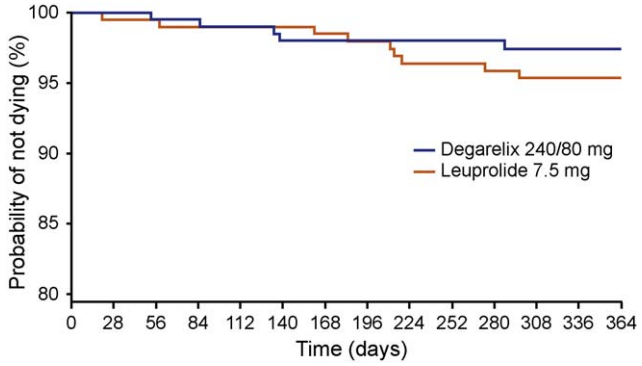


**Fig. 2 – Overall survival by treatment (intent-to-treat population).**

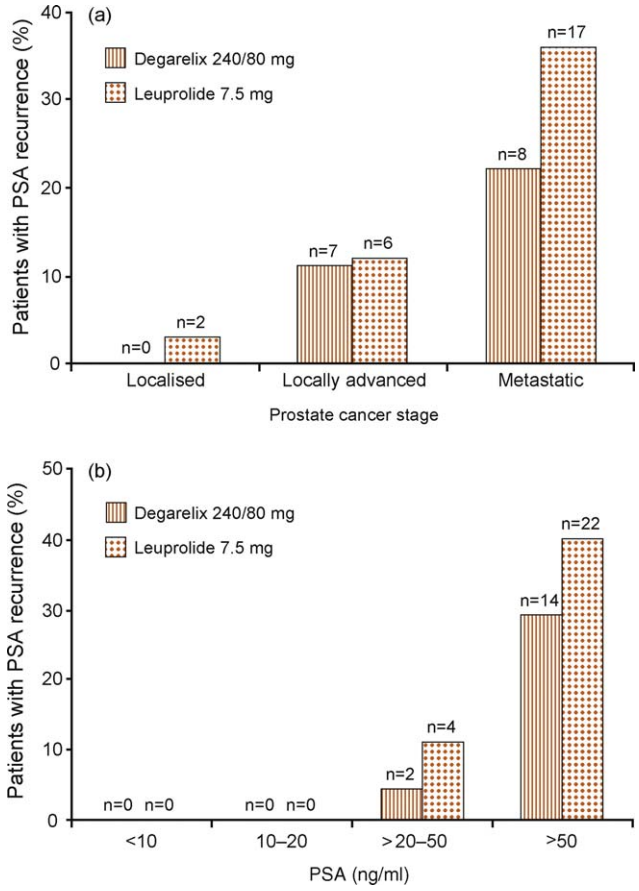


**Fig. 3 – Prostate-specific antigen (PSA) recurrence during the course of the study by baseline (a) disease stage or (b) PSA level.**

proportion of degarelix patients experienced PSA recurrence in the locally advanced subgroup compared with leuprolide.

PSA recurrence occurred more frequently in patients with higher baseline PSA in both treatment groups; all recurrences occurred in those with baseline PSA >20 ng/ml (Fig. 3b). In patients with baseline PSA >20 ng/ml, risk of PSA recurrence was significantly lower for patients receiving degarelix ($p = 0.04$; Fig. 4b). In patients with baseline PSA >50 ng/ml, 29.2% of those receiving degarelix and 40.0% of those receiving leuprolide experienced PSA recurrence ($p = 0.10$).

### *3.4. Prostate-specific antigen levels over time by baseline disease stage*

There was a faster initial suppression of PSA levels with degarelix 240/80 mg compared with leuprolide, irrespective of baseline disease stage. An initial increase in PSA observed in patients with metastatic disease receiving leuprolide was not seen in the degarelix group. The proportion of patients achieving PSA suppression <4 ng/ml at day 28 was 59% versus 34% in the degarelix and leuprolide groups, respectively ($p < 0.0001$). At day 364, corresponding proportions were 83% and 78% ($p = 0.339$). Overall, the proportion of patients achieving PSA < 4 ng/ml over time was similar in both treatment groups, although achievement of PSA <4 ng/ml was faster with degarelix (Fig. 5). For patients with metastatic disease, a higher proportion of those receiving degarelix achieved PSA <4 ng/ml over the duration of the study.

## 4. Discussion

PSA recurrence may be used as a method for determining disease recurrence following definitive prostate cancer therapy, and given the protracted natural history, PSA is frequently used for identifying treatment failure in all disease stages [12]. PSA recurrence often precedes clinically detectable recurrence by years, and the size/velocity of the increase may be helpful when considering the need for further treatment. The value of PSA recurrence rate and time to recurrence is often debated when it comes to performing interim analyses of hormonal therapy efficacy. Data from the bicalutamide trial programme showed a modest correlation between time to PSA progression and objectively confirmed progression [13]. In metastatic prostate cancer, several studies demonstrated some level of association between post-therapy falls in PSA or PSA relapse and long-term prognosis, but none confirmed PSA could be used as surrogate end points [14–18]. Recent

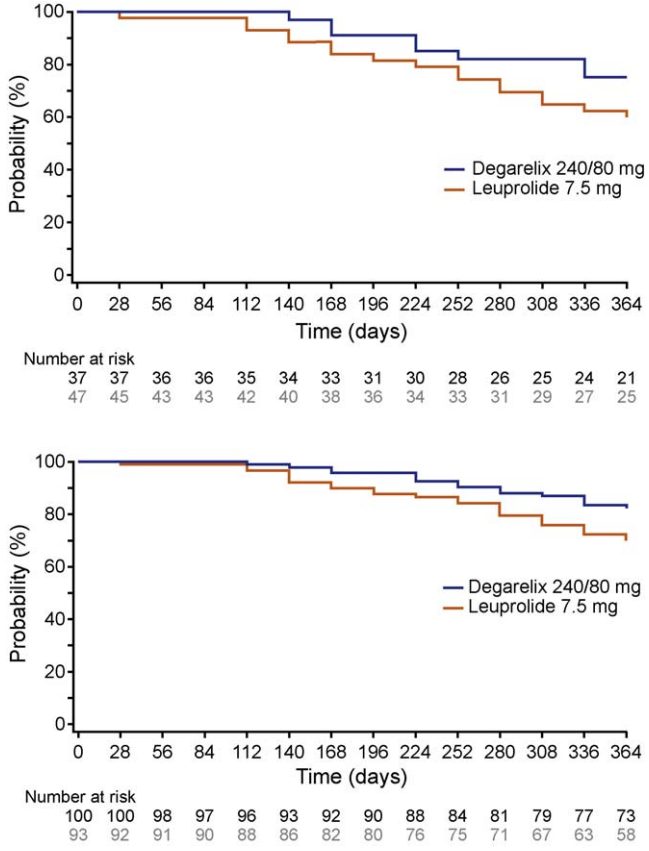


**Fig. 4 – Probability of being free from prostate-specific antigen (PSA) recurrence in patients with baseline (a) metastatic disease or (b) PSA >20 ng/ml.**

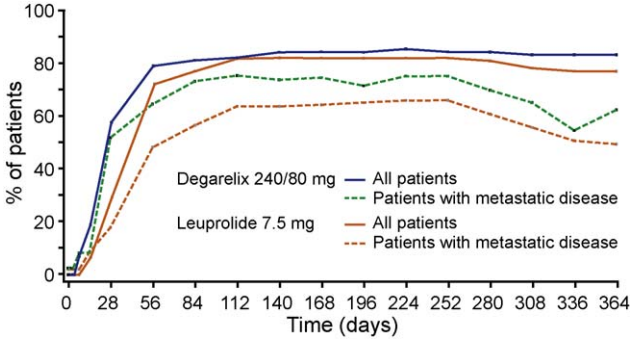


**Fig. 5 – Proportion of patients with prostate-specific antigen <4 ng/ml over time overall and in those with metastatic disease at baseline.**

analyses, however, provide a different view. Data from 1078 patients with hormone-sensitive prostate cancer included in the Southwest Oncology Group trial 9346 showed that PSA progression (increase of ≥25% from nadir and an absolute increase of ≥2 or 5 ng/ml) predicts overall survival and may therefore be a suitable end point for studies in similar settings [10].

It is interesting that the overall probability of PSA recurrence was lowest in the degarelix 240/80 mg group (8.9%) and similar between those receiving degarelix 240/160 mg and leuprolide (14.2% vs 14.1%, respectively) [11]. The reason for this is unknown; however, it may be related to the fact that a slightly higher proportion of patients in the degarelix 240/160 mg group had baseline PSA >50 ng/ml, which might indicate a likelihood of poorer outcome with respect to the PSA recurrence end point. In addition, it may be related to the fact that the bioavailability of degarelix appears to be concentration dependent. Because the 160 mg (40 mg/ml) and 80 mg (20 mg/ml) maintenance doses are administered at different concentrations, it is possible that any resultant differences in maximal drug concentration or area under the curve could affect the activity of the drug (although testosterone control appeared similar for the two doses). PSA recurrences in this trial occurred mainly in patients with locally advanced or metastatic disease, as would be expected in a study lasting 1 yr. PSA recurrences also occurred exclusively in patients with baseline PSA >20 ng/ml. Associations between disease stage, pretreatment PSA level, and risk of PSA recurrence and/or clinical outcome have been reported previously [8,19–24]. In the present analyses, patients with baseline PSA >20 ng/ml had a significantly lower risk of PSA recurrence with degarelix 240/80 mg compared with leuprolide ($p = 0.04$); however, it is possible this could be partly due to differences in baseline characteristics between subgroups because this was an unadjusted analysis. Patients in the intent-to-treat population also had a statistically lower risk of PSA recurrence or death with degarelix compared with leuprolide ($p = 0.05$; log-rank). Adjusting for baseline disease stage and PSA level still retained a HR of 0.664 (95% CI, 0.385–1.146). Several hypotheses may explain why there may be longer-term differences in agonist and antagonist activity. One is that the initial testosterone surge that is thought only to have acute consequences might also have longer-term effects on tumour control. A second possibility is the occurrence of testosterone microsurges following GnRH agonist readministration. In CS21 no patients in the degarelix group had microsurges compared with 4% of those in the leuprolide group [11]. It was shown in one study that breakthrough increases in testosterone can adversely affect progression-free survival [25]. Another mechanism may be an additional effect of degarelix mediated directly at the level of GnRH receptor expression in prostate cancer cells [26]. Finally, a potential reason for this difference may relate to the fact that antagonists suppress FSH levels more effectively than agonists [11], and preclinical evidence suggests that FSH signalling contributes to the progression of castration-resistant prostate cancer [27].

The definition of PSA recurrence used in the current analyses was chosen because of the mixed population included in this study, and it is more stringent than many others used in the literature. It should therefore provide robust evidence of biochemical recurrence in this population. It is very similar to the criteria defined by the first Prostate Cancer Working Group (PCWG1) that were in use when the trial was designed. Indeed, PCWG1 recommended that in patients whose sole manifestation of disease progression was a rising PSA level, a sequential rise in PSA measured at least 1 wk apart should be obtained and

that the minimum threshold level for PSA progression be 5 ng/ml. After the CS21 trial had completed, PCWG2 redefined PSA progression as a 25% increase from the baseline value along with an increase in absolute value of ≥2 ng/ml after 12 wk of treatment [28].

Where differences in initial PSA suppression were identified, these favoured degarelix over leuprolide in both the primary and exploratory analyses. In the primary analysis, significantly greater PSA reductions were seen at days 14 and 28 with degarelix versus leuprolide [11]. After 14 d of treatment, PSA levels had declined by 64% versus 18% in these groups, respectively ($p < 0.001$). This contrasts with data for the only other marketed GnRH antagonist, abarelix, where no PSA responses (≥50% reduction in PSA levels from baseline) were observed at this time point in two small studies [29,30]. In addition, degarelix monotherapy provided a similar rate of PSA decrease to that observed in patients receiving leuprolide plus concomitant antiandrogen [11].

In the exploratory analyses, degarelix patients generally achieved more rapid PSA control compared with leuprolide, irrespective of baseline disease stage and PSA level. An increasing proportion of patients in both groups achieved PSA <4 ng/ml or <0.2 ng/ml over the course of this 1-yr study, although overall, a higher proportion of degarelix patients with metastatic disease achieved these criteria compared with leuprolide. The significant difference in the proportion of patients achieving PSA <4 ng/ml at day 28 indicates the more rapid onset of action of degarelix. This can be explained by the different modes of action of these two agents: leuprolide causes a transient increase in testosterone, whereas degarelix immediately blocks GnRH receptors and rapidly reduces testosterone levels. Despite the relatively small numbers of patients in each subgroup, overall these data generate the hypothesis that PSA control may be improved with degarelix, particularly in the advanced disease setting. The consistency of results across the different analyses supports this finding. The duration of follow-up may be viewed as a limitation; however, this is the standard time required for a trial of this type. It is also worth noting that 26 of 93 patients (28%) with baseline PSA >20 ng/ml in the leuprolide group had experienced PSA recurrence after 1 yr, which is in line with reported figures in the literature.

Several previous studies have suggested that improved PSA control has a positive impact on overall survival [8,9,10,23]. In the Southwest Oncology Group trial S9346, achievement of PSA ≤4 ng/ml after 7 mo of treatment was associated with significantly improved survival compared with PSA >4 ng/ml ($p < 0.001$) in men with hormone-sensitive prostate cancer [9]. Median survival was 13 mo for patients with PSA >4 ng/ml, 44 mo for PSA 0.2–4 ng/ml, and 75 mo for patients with PSA <0.2 ng/ml. A more recent analysis of data from S9346 and a second similar trial (S9916) performed in men with castrate-resistant disease demonstrated a significant association between PSA progression and overall survival, irrespective of the PSA progression definition used [10]. In S9346, median overall survival was 10 mo versus 44 mo for patients who did and did not have PSA progression at 7 mo; in S9916, median overall survival was 11 mo versus 18 mo for those who did and did not have PSA progression at 3 mo. At the time of the present analysis, overall survival was still high in the degarelix 240/80 mg and leuprolide groups. Longer follow-up is required to determine if any differences between treatments translate into survival benefits.

## 5. Conclusions

In summary, the results of these exploratory analyses generate the hypothesis that patients in the CS21 study had improved PSA control with degarelix 240/80 mg compared with leuprolide 7.5 mg/mo. The difference in this 1-yr study was most marked in those with metastatic prostate cancer or high baseline PSA levels. Further studies with longer follow-up are warranted to confirm these findings, to evaluate their clinical significance, and to follow PSA control in patients with earlier, more slowly progressing disease.

***Author contributions:*** Bertrand 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.

*Study concept and design:* Tombal, Schröder, Boccon-Gibod, Miller, Shore, Kold Olesen, Persson.
*Acquisition of data:* Crawford, Moul.
*Analysis and interpretation of data:* Tombal, Schröder, Crawford, Miller, Boccon-Gibod, Moul, Shore, Jensen, Kold Olesen, Persson.
*Drafting of the manuscript:* Tombal, Schröder, Crawford, Shore, Kold Olesen, Persson.
*Critical revision of the manuscript for important intellectual content:* Tombal, Schröder, Crawford, Moul, Shore, Kold Olesen, Persson.
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