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Degarelix vs leuprolide treatment in patients with advanced prostate cancer: PSA failures during a randomised, phase III trial (CS21)

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INTRODUCTION

Prostate-specific antigen (PSA) is a commonly used marker in screening for prostate cancer and for monitoring response to treatment as well as disease recurrence and progression[1,2]

Degarelix is a gonadotrophin-releasing hormone (GnRH) receptor blocker that achieves androgen deprivation in the treatment of hormone-sensitive prostate cancer. Degarelix has an immediate onset of action that results in fast testosterone suppression,[3,4] without inducing an initial testosterone surge as seen during GnRH receptor agonist treatment[5]

A randomised phase III trial (CS21) recently compared the efficacy and safety of degarelix with leuprolide in the treatment of prostate cancer.[6] Degarelix displayed significantly faster luteinising hormone, follicle-stimulating hormone, testosterone and PSA suppression, and was at least as effective as leuprolide with respect to the primary endpoint – suppression of testosterone to castrate levels over the 12-month study period. Here we report further PSA sub-analyses from the CS21 trial, including the secondary endpoint, PSA failures

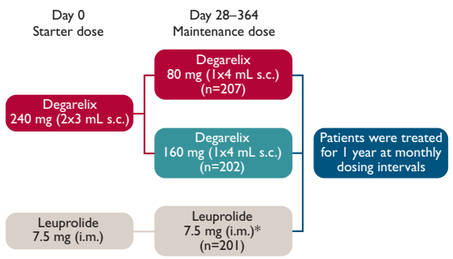
METHODS

Study design

This was a 1-year, multicentre, phase III, randomised, open-label, parallel-group trial powered to demonstrate non-inferiority of degarelix vs leuprolide for the primary endpoint (proportion of patients with testosterone ≤0.5 ng/mL at each monthly measurement for 1 year). Patients were randomised to one of three treatment groups (Figure 1). Bicalutamide could be given as flare protection to patients in the leuprolide group

FIGURE 1

CS21 study design



Patient visits:
Day 0, 1, 3, 7, 14, 28, 56... (+28) ...364
Additional visits occurred after Day 3 and Day 7 following the 9th dose
*Anti-androgen was allowed at the discretion of the investigator

Patients

Patients with histologically confirmed adenocarcinoma of the prostate (all stages), for whom androgen deprivation therapy was indicated, were eligible for the study. This included patients with rising PSA after prostatectomy or radiotherapy of curative intent. Patients requiring neoadjuvant hormonal therapy were not eligible. Patients were also required to have serum testosterone levels >1.5 ng/mL, an Eastern Cooperative Oncology Group performance status ≤2 and PSA ≥2 ng/mL

PSA analyses

PSA failure (a secondary endpoint) was defined as two consecutive increases in PSA of 50% compared with nadir and ≥5 ng/mL on two consecutive measurements at least 2 weeks apart; the endpoint being recorded on the date of the second measurement. 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 occurrence of PSA failure or death. PSA failures were also analysed by disease stage and baseline PSA level. Only the degarelix 240/80 mg dose was used in these sub-analyses as this dose was recently approved by the FDA and EMEA for the treatment of advanced prostate cancer

RESULTS

Patients

In total, 610 patients were treated and baseline characteristics were similar between groups (Table 1). Approximately 50% of patients had locally advanced (29.2%) or metastatic (20.5%) disease at baseline and overall, median age was 73 years, median testosterone was 3.93 ng/mL and median PSA was 19.0 ng/mL

TABLE 1

Baseline characteristics (intent-to treat [ITT] population)

	Degarelix 240/80 mg	Degarelix 240/160 mg	Leuprolide 7.5 mg
ITT analysis set, n	207	202	201
Median age, years (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	37 (18)	41 (20)	47 (23)
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)

[a]Localised: T 1/2, NX or N0, and M0; [b]Locally advanced: T 3/4, NX or N0, and M0, or N1 and M0

PSA failure – overall analysis

The overall incidences of PSA failure and death are shown in Table 2. The probability of completing the study without experiencing PSA failure by Day 364 was 91.1% (95% CI: 85.9–94.5) for the degarelix 240/80 mg group and 85.9% (95% CI: 79.9–90.2) for the leuprolide group. The overall probability of completing the study without dying by Day 364 was 97.4% (95% CI: 93.8–98.9) in the degarelix 240/80 mg group and 95.1% (95% CI: 90.7–97.4) in the leuprolide group

TABLE 2

Overall incidence and probability of PSA failure or death

	Degarelix 240/80 mg (n=207)	Degarelix 240/160 mg (n=202)	Leuprolide 7.5 mg (n=201)
Incidence of PSA failure, n (%)	16 (7.7)	26 (12.9)	26 (12.9)
Probability of PSA failure,[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)

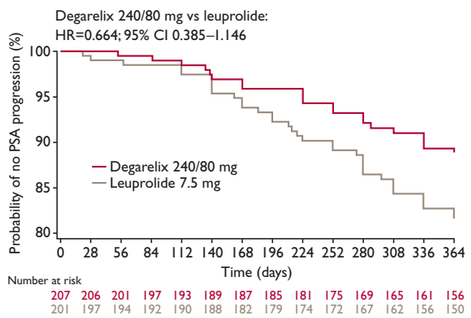
[a]Probability of experiencing PSA failure or death by Day 364 (estimated using the Kaplan-Meier method)

PSA progression-free survival

Degarelix 240/80 mg was associated with longer PSA progression-free survival compared with leuprolide 7.5 mg (Figure 2)

FIGURE 2

PSA progression-free survival (ITT population)



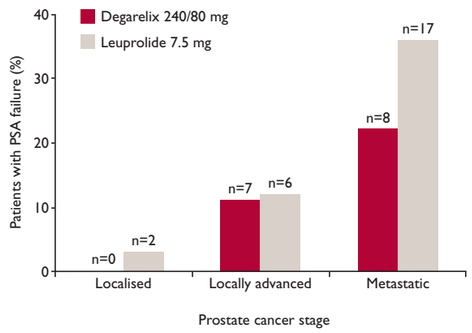
HR, hazard ratio

PSA failure – by baseline disease stage

PSA failure occurred more frequently in patients with advanced disease, in both treatment groups; the majority of PSA failures occurred in patients with metastatic disease at baseline (Figure 3). In the subgroup of 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 failure (p=0.1559)

FIGURE 3

Incidence of PSA failure by baseline disease stage (ITT population)

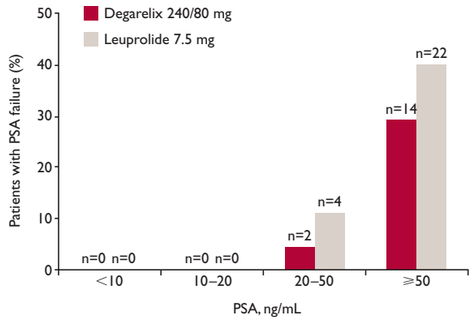


PSA failure – by baseline PSA level

PSA failure occurred more frequently in patients with higher baseline PSA level, in both treatment groups; all the PSA failures occurred in patients with baseline PSA ≥20 ng/mL (Figure 4). In the subgroup of patients with baseline PSA ≥50 ng/mL, 29.2% of those in the degarelix 240/80 mg group and 40.0% of those in the leuprolide group experienced PSA failure (p=0.10)

FIGURE 4

Incidence of PSA failure by baseline PSA level (ITT population)



In the subgroup of patients with baseline PSA ≥20 ng/mL, time to PSA failure was significantly longer for patients receiving degarelix 240/80 mg (p=0.0436; Figure 5)

Overall survival

Overall survival was not statistically significantly different between the degarelix 240/80 mg and leuprolide groups (Figure 6)

FIGURE 5

PSA failure in patients with baseline PSA ≥20 ng/mL

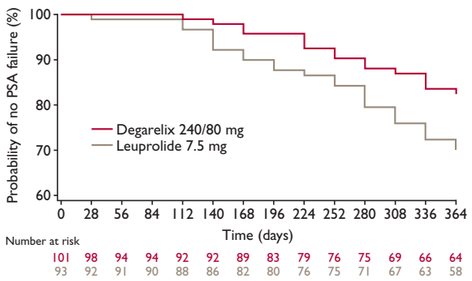
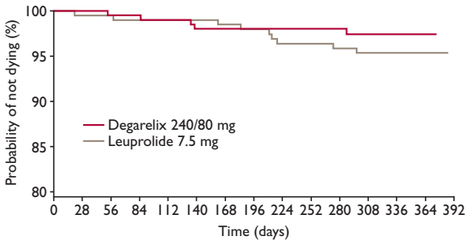


FIGURE 6

Overall survival by treatment (ITT population)



CONCLUSIONS

- PSA failures occurred mainly in patients with locally advanced or metastatic disease as would be expected in a study of 1 years' duration
- Patients in the full ITT population had a significantly longer time to PSA failure or death with degarelix 240/80 mg compared with leuprolide
- PSA failure events occurred exclusively in patients with PSA ≥20 ng/mL at baseline. These patients had a significantly longer time to PSA failure with degarelix 240/80 mg compared with leuprolide
- Further studies with longer follow-up are warranted to confirm these findings and to follow PSA control in patients with earlier and more slowly progressing disease

References

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