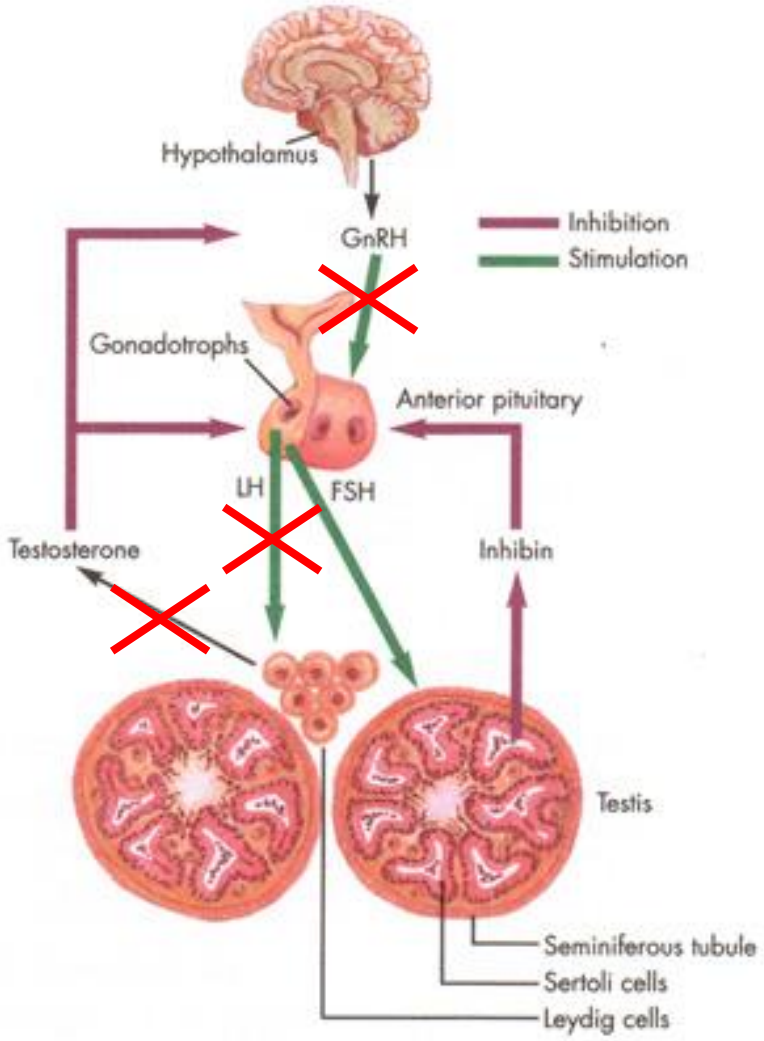
GnRH antagonists

דר' איתי שטרנברג

Hormonal axis



GnRH

- Decapeptide
- Pulsatile secretion by hypothalamic neurons
- Short half-life (2-5 min)
- Stimulates gonadotropins secretion from the anterior pituitary

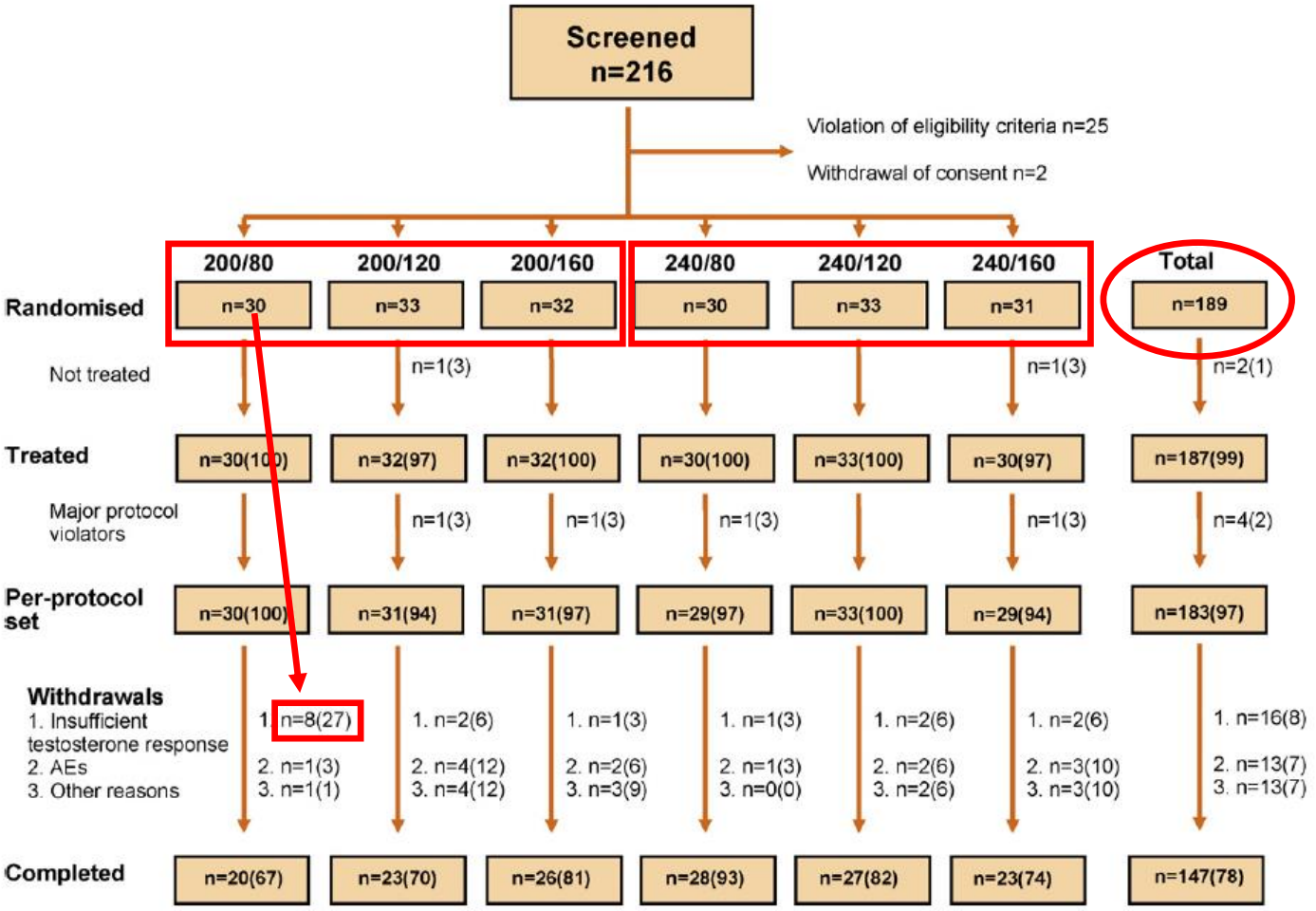
GnRH agonists

Amino acid number	1	2	3	4	5	6	7	8	9	10
Native LHRH	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	Gly-	Leu-	Arg-	Pro-	Gly-NH2
Leuprolide	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	D-Leu-	Leu-	Arg-	Pro-	Ethylamide
Goserelin	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	D-Ser(tBu)-	Leu-	Arg-	Pro-	Gly-NH2
Triptorelin	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	D-Trp-	Leu-	Arg-	Pro-	Gly-NH2
Histrelin	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	D-His(Imbzl)	Leu-	Arg-	Pro-	N-Et-NH2

GnRH antagonists

Amino acid number	1	2	3	4	5	6	7	8	9	10
Native LHRH	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	Gly-	Leu-	Arg-	Pro-	Gly-NH2
Abarelix	Ac-DNal	DCpa-	DPal-	Ser-	NaMeTyr	DAsp	Leu-	Ilys	Pro-	DAla
Cetrorelix	Ac-DNal	DCpa-	DPal-	Ser-	Tyr-	DCit	Leu-	Arg-	Pro-	DAla
Ganirelix	Ac-DNal	DCpa-	DPal-	Ser-	Try-	DHar(Et2)	Leu-	Har(Et2)	Pro-	DAla
Degarelix	Ac-DNal	DCpa-	DPal-	Ser-	Aph(Hor)	D4Aph(Cbm)	Leu-	Ilys	Pro-	DAla

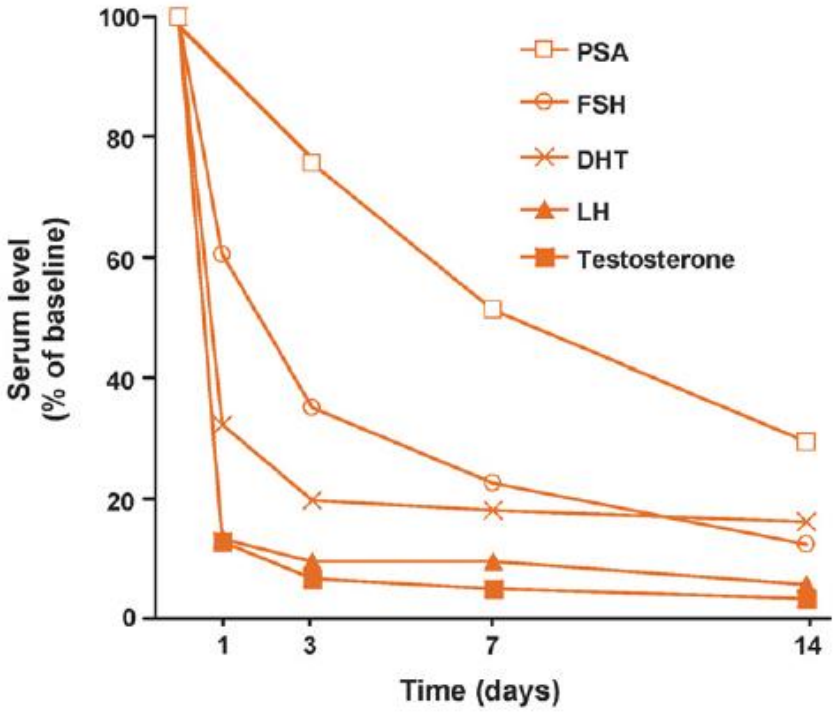
Phase 2 Dosage-Finding Study in the Treatment of CaP with Degarelix



Van Poppel et al. Eur Urol 2008; 54: 805-815

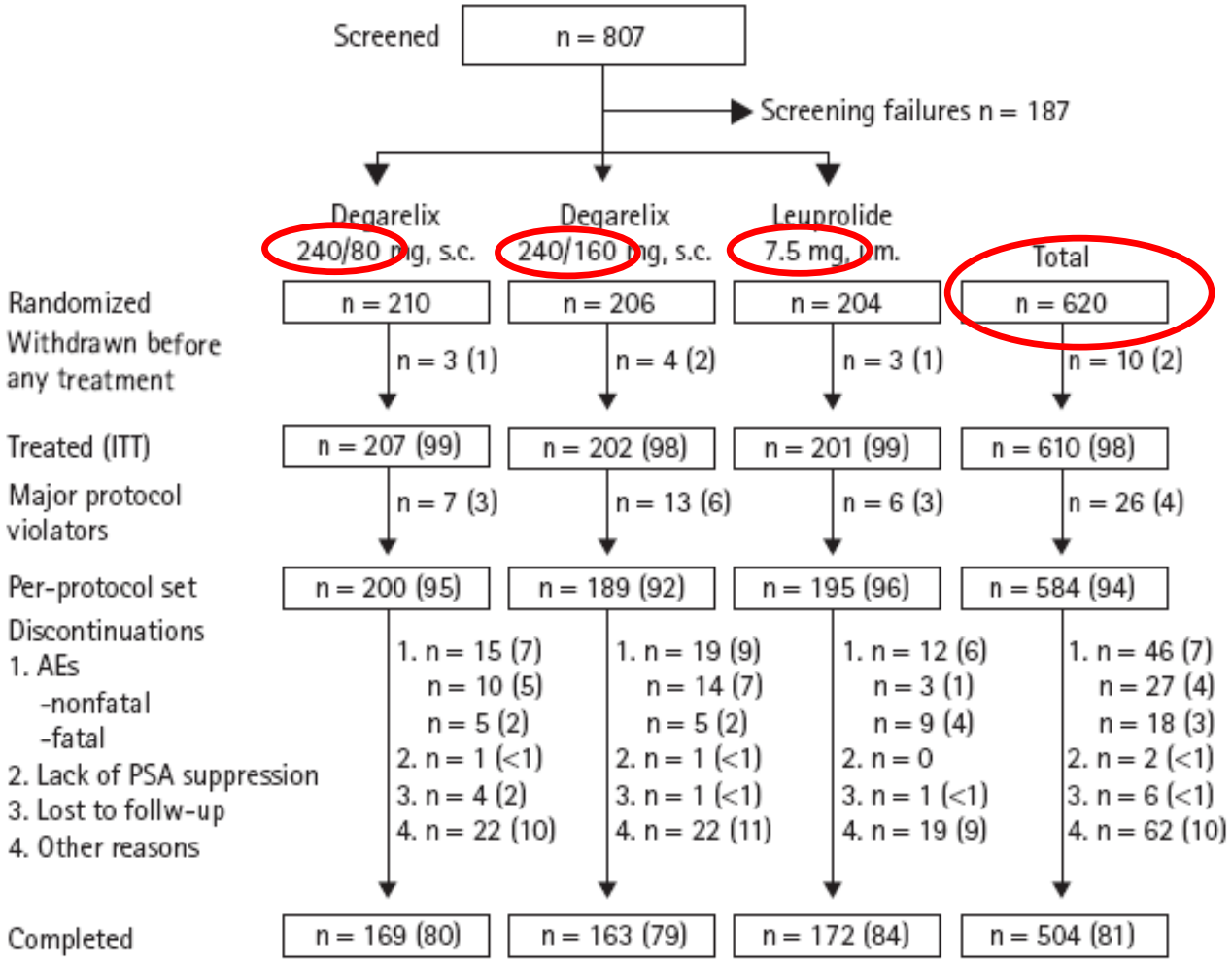
Phase 2 Dosage-Finding Study in the Treatment of CaP with Degarelix

- Preferred initial dose of 240mg
- Monthly preferred dose of 160mg
- AEs mainly related to androgen deprivation
- No dose dependent side effects
- No systemic reactions



Van Poppel et al. Eur Urol 2008; 54: 805-815

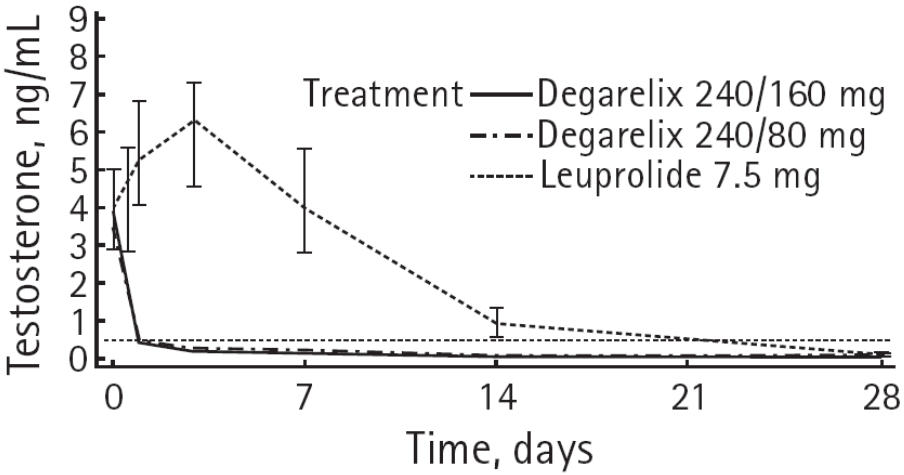
Phase III Study – Degarelix for Prostate Cancer



Klotz et al. BJUI 2008; 102: 1531-1538

Testosterone suppression

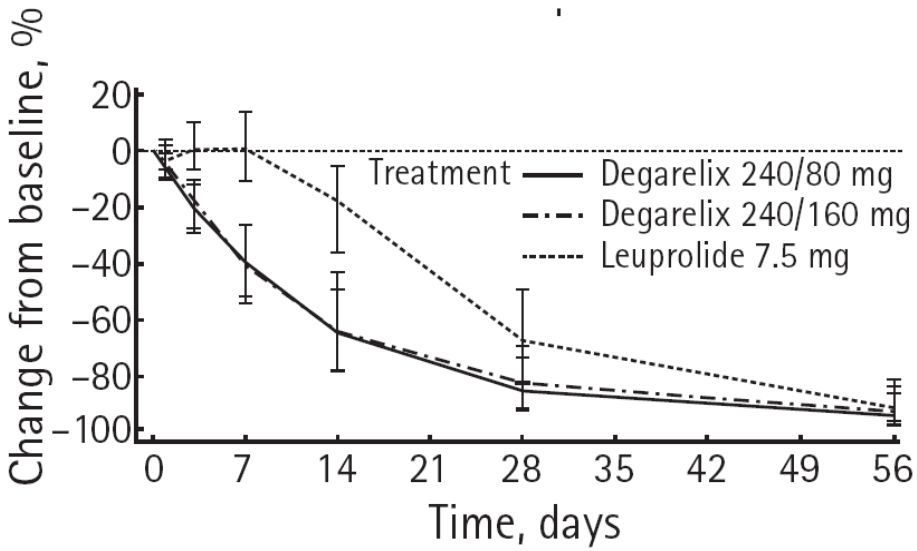
- Day 3
  ↓95.5-96.1% degarelix
  ↑65% leuprolide
  (P<0.001)
- T>0.5ng/ml until day 28 in leuprolide



Klotz et al. BJUI 2008; 102: 1531-1538

PSA suppression

- 14 days
  64-65% degarelix
  18% leuprolide
- 28 days
  83-85% degarelix
  68% leuprolide
- P<0.001 (both)



Klotz et al. BJUI 2008; 102: 1531-1538

GnRH Agonist/Antagonist comparison

	GnRH agonists	GnRH antagonists
LH surge	+	-
Time to castration	14-21 days	1-3 days
Microsurges	+	-
FSH secretion	+	-
AEs	UTIs, Arthralgia	Histamine, Chills

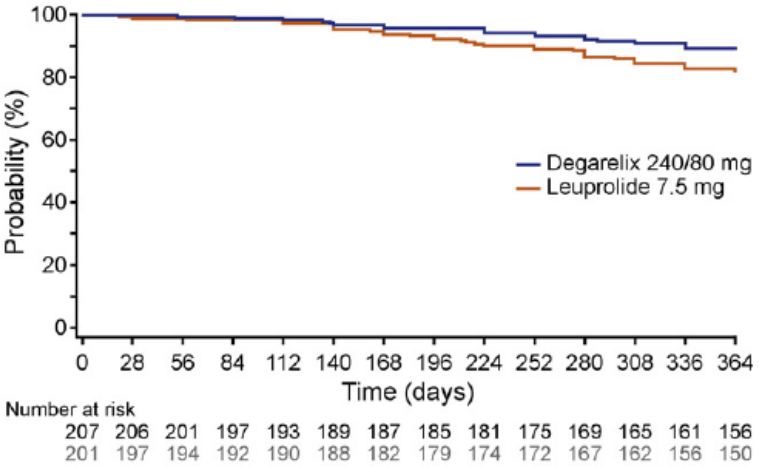
Testosterone level and Degarelix

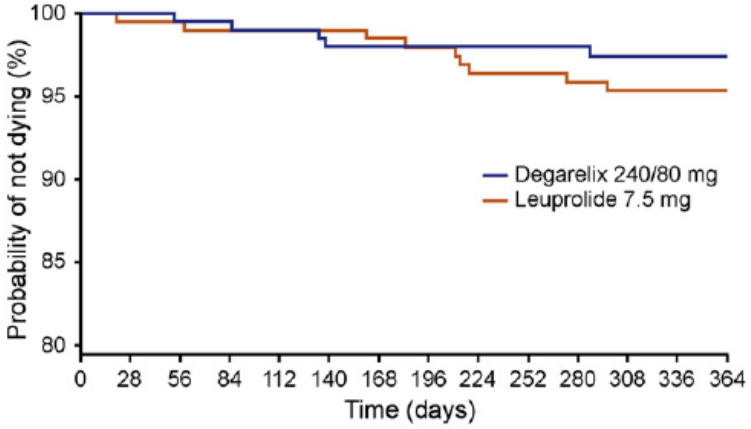
- Higher T → Longer time to T≤0.5ng/ml
- Reduction of T to castrate level faster with Degarelix
- Small increase in PSA on days 3 and 7 in Leuprolide group
- PSA increase larger in subgroup of patients with baseline T≥5ng/ml

Damber et al. Eur Urol Suppl 2009; 8: 130 (EAU abstract)

Biochemical Failure and Survival

- PSA recurrence
  Degarelix 7.7%
  Leuprolide 12.9%
- Patients receiving Degarelix have a lower risk of PSA recurrence and death (p=0.05)

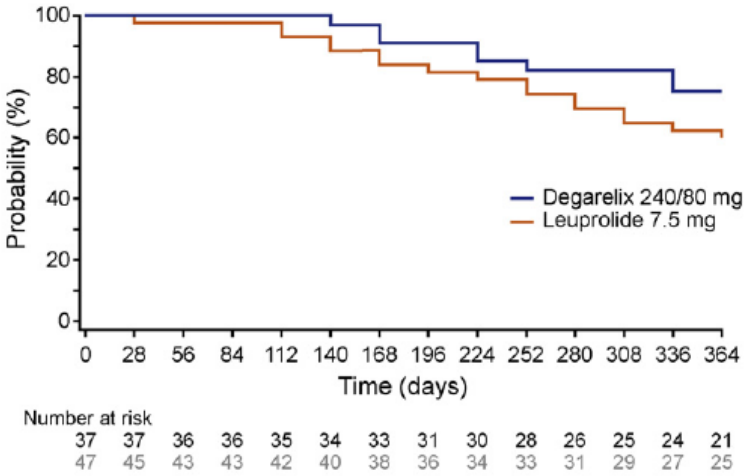




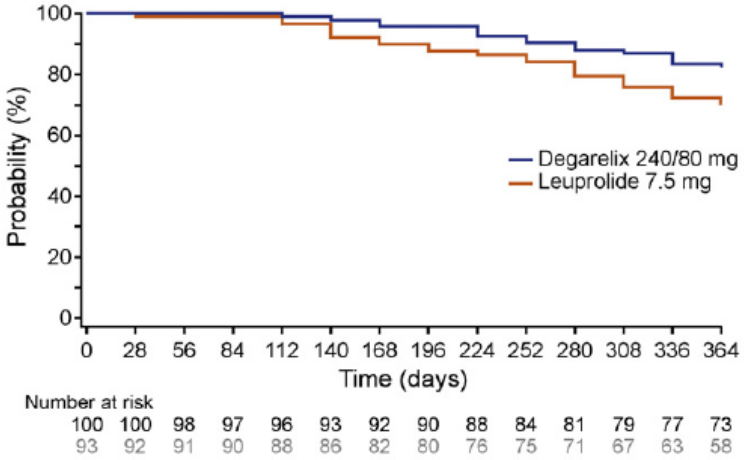
Tombal et al. Eur Urol (2009),doi:10.1016/j.eururo.2009.11.029

Biochemical Failure and Survival

- PSA recurrence in metastatic disease
  Degarelix 21.6%
  Leuprolide 36.2%
  (p=0.156)



- Baseline PSA≥20ng/ml
  PSA recurrence lower in Degarelix group (p=0.04)



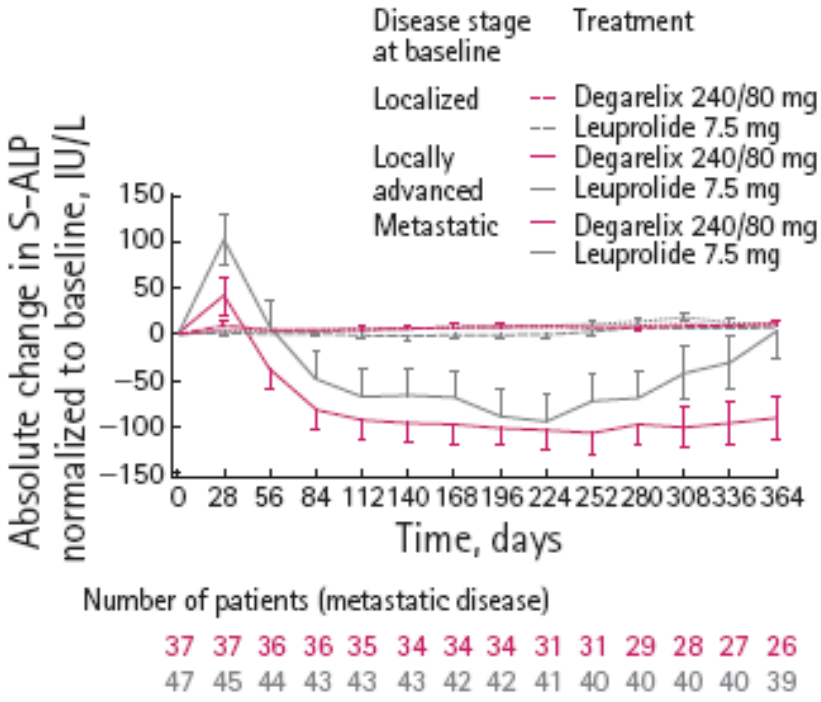
Tombal et al. Eur Urol (2009),doi:10.1016/j.eururo.2009.11.029

Alkaline Phosphatase level and Degarelix

- Earlier ALP supression in Degarelix group
- No late rise in ALP in Degarelix group

? No T surge and microsurges

? Better FSH reduction



Schröder et al. BJUI (2009); doi:10.1111/j.1464-410X.2009.08981.x

Potential advantages for GnRH antagonists

- No flare
  (bone pain, BOO, obstructive renal failure, spinal cord compression, pathologic fractures)
- Baseline T ≥5ng/ml
- PSA >20ng/ml
- Elevated Alkaline Phosphatase (Hb<13gr/dL)

GnRH (Cetrorelix) for BPH

(A)	Dosage regimens			
Week −4, −3, −2, and −1	Placebo run-In (PLA: 2 ml × 2; weekly × 4)			
Week 0	Randomized treatment allocation			
	PLA	CET 4 × 5	CET 2 × 10	CET 4 × 10
Week 0	PLA 2 ml × 2	CET 5 mg PLA 2 ml	CET 5 mg × 2	CET 5 mg × 2
Week 1	PLA 2 ml × 2	CET 5 mg PLA 2 ml	PLA 2 ml × 2	CET 5 mg × 2
Week 2	PLA 2 ml × 2	CET 5 mg PLA 2 ml	CET 5 mg × 2	CET 5 mg × 2
Week 3	PLA 2 ml × 2	CET 5 mg PLA 2 ml	PLA 2 ml × 2	CET 5 mg × 2

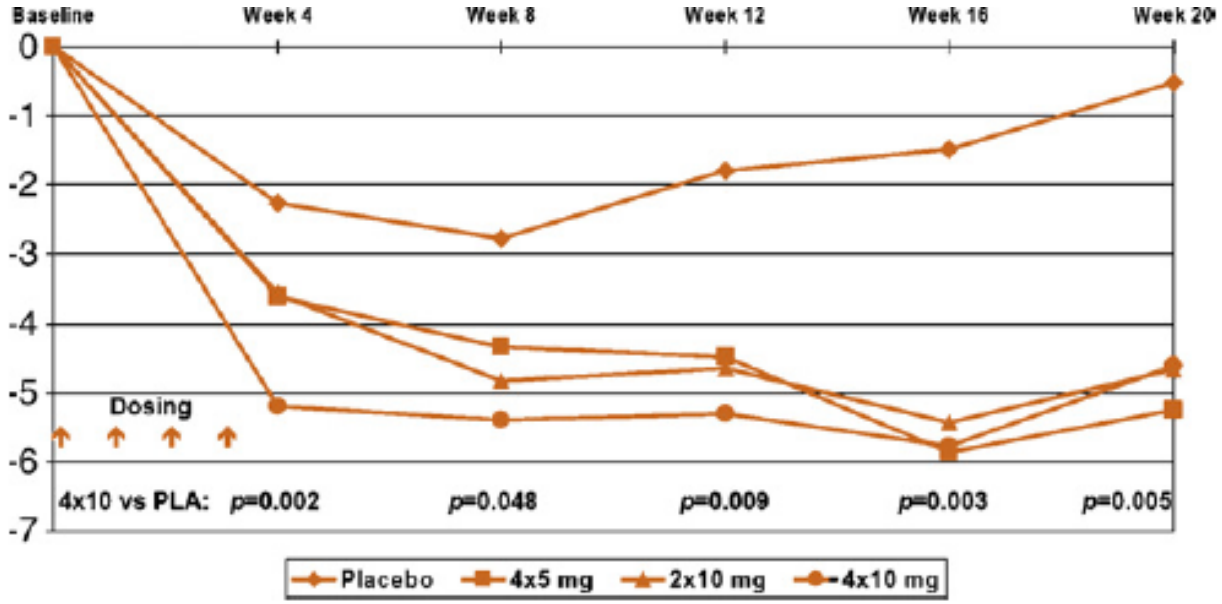
(B)	No. of patients			
Screened	140			
	PLA	CET 4 × 5	CET 2 × 10	CET 4 × 10
Treatment allocated	35	35	35	35
Treatment completed	35	35	35	34 (−1*)
Evaluable at W12	35	35	33 (−2†)	32 (−3†)
Evaluable at W20	34	33	32 (−3‡)	32 (−3)
Evaluable for safety	35	35	35	35

PLA = placebo; CET = cetrorelix; W = week.
* Withdrawn after first dose due to concomitant condition.
† Two patients each lost to follow-up after end of treatment.
‡ One patient lost to follow-up between W12 and W20.

Debruyne et al. Eur Urol 2008; 54: 170-180

IPSS improvement with Cetrorelix

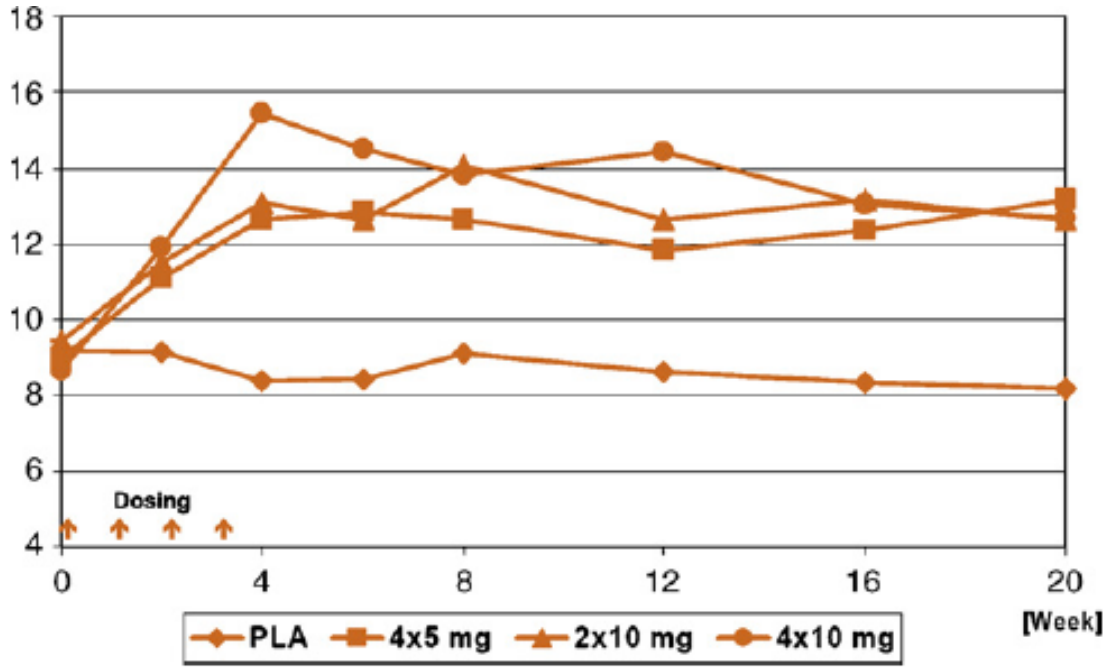
- Significant reduction of IPSS in CET groups
- Continuous improvement



Debruyne et al. Eur Urol 2008; 54: 170-180

Max Flow improvement with Cetrorelix

- Significant Vmax increase in CET groups
- Vmax unchanged in placebo group



Debruyne et al. Eur Urol 2008; 54: 170-180

GnRH (Cetrorelix) for BPH

- Prostate volume reduction in all groups
- No indications for treatment-related differences in sexual function
- All groups showed improved QOL
- No local site reactions
- No systemic castration-like subjective side effects

Debruyne et al. Eur Urol 2008; 54: 170-180