LASER TRAINING DAYS

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19 - 20 GIUGNO 2019

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Long Acting LHRH

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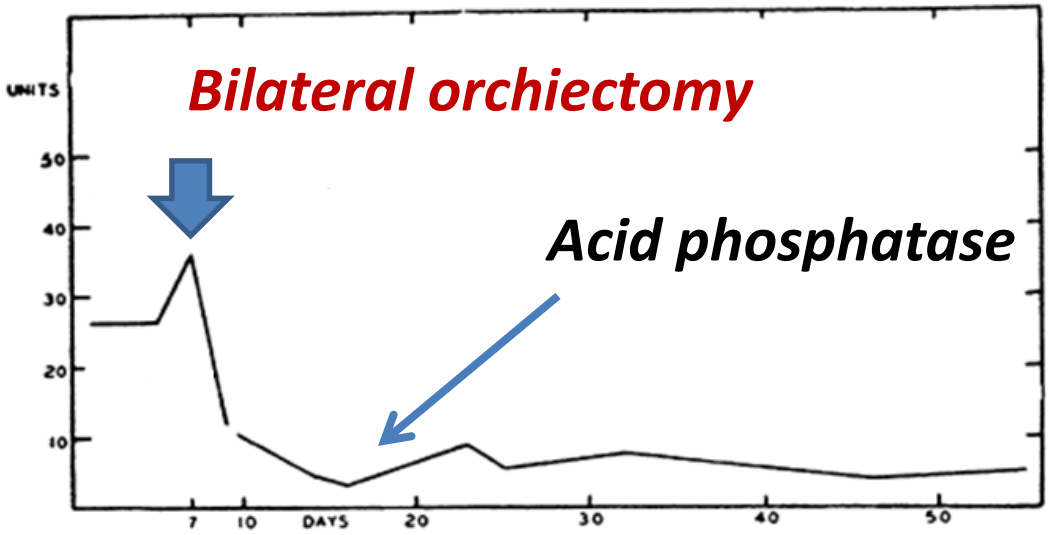
Pre-PSA era

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

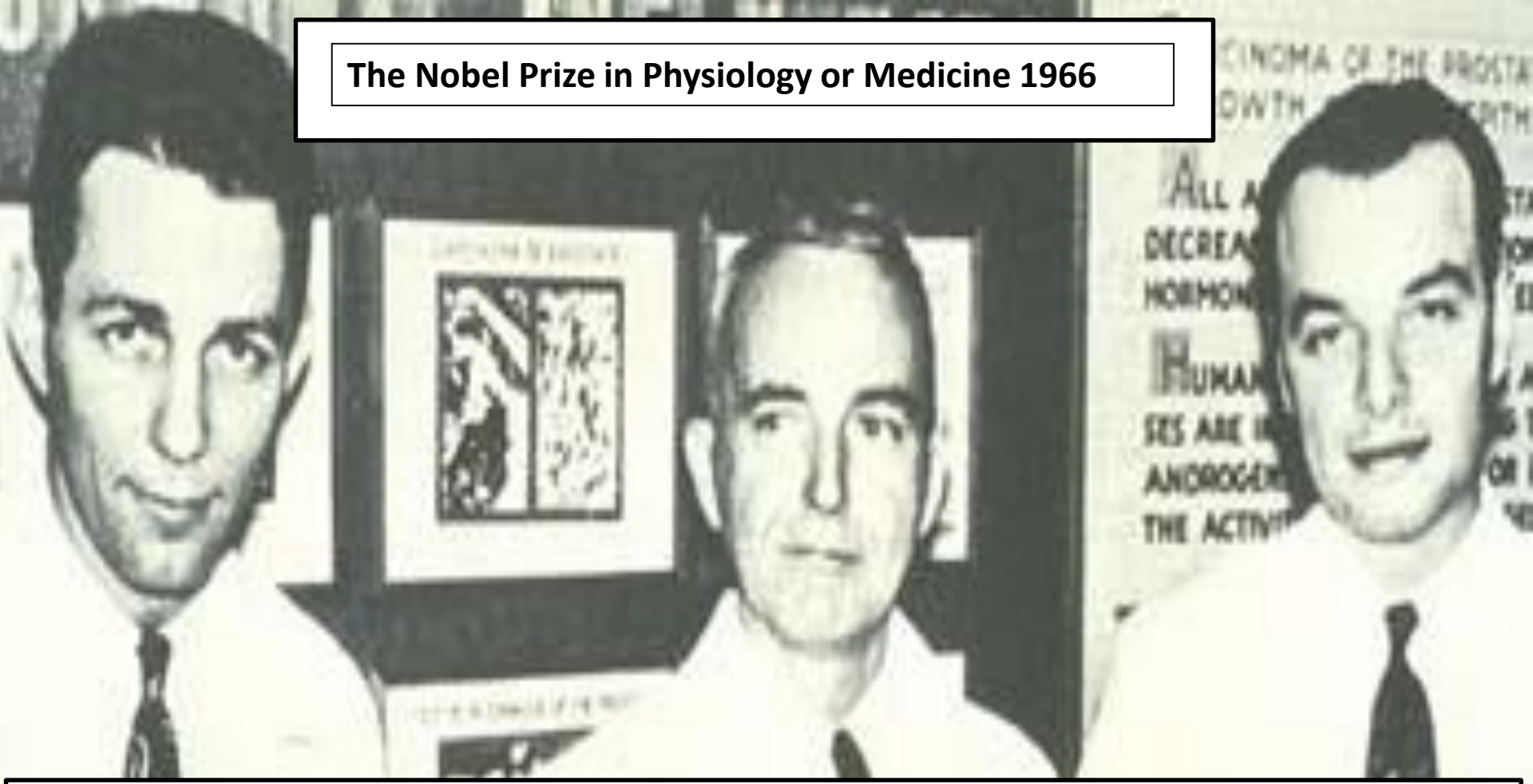
(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

1941



Charles B. Huggins, M.D. (1901-1997)

The Nobel Prize in Physiology or Medicine 1966



Dr. Huggins, in collaboration with his students Clarence V. Hodges and William Wallace Scott, published three papers in 1941 that demonstrated the relationship between the endocrine system and the normal functioning of the prostate gland. They also showed that by blocking the male hormones that were involved in prostate function--through removal of the testicles or administration of estrogens which would neutralize the male hormones--they could cause regression of prostate tumors.

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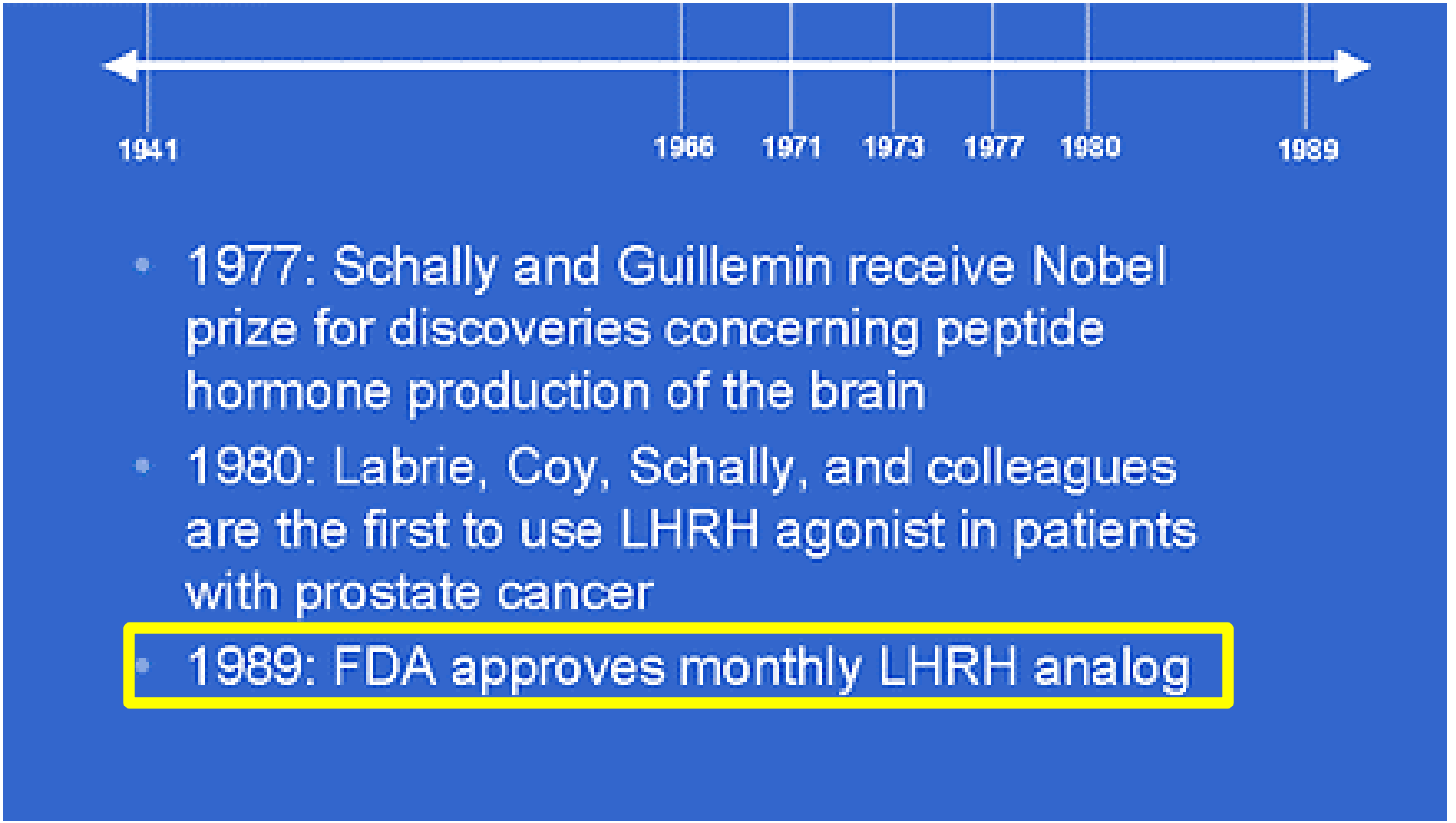
ADT: Where we have come from



Medscape O.Sartor

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Optimal Testosterone control in Pca

1. ***Food and Drug Administration , 1980***

Similarly to the experts, a large group of delegates at the 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases confirmed that achieving "the lowest testosterone level possible" is their main goal of hormone therapy. 64% of this group agreed that they would consider a castrate level of below or equal to 20 ng/dL to be optimal.

2. ***Zlotta A., et al., Eur Urol Suppl, 2005***

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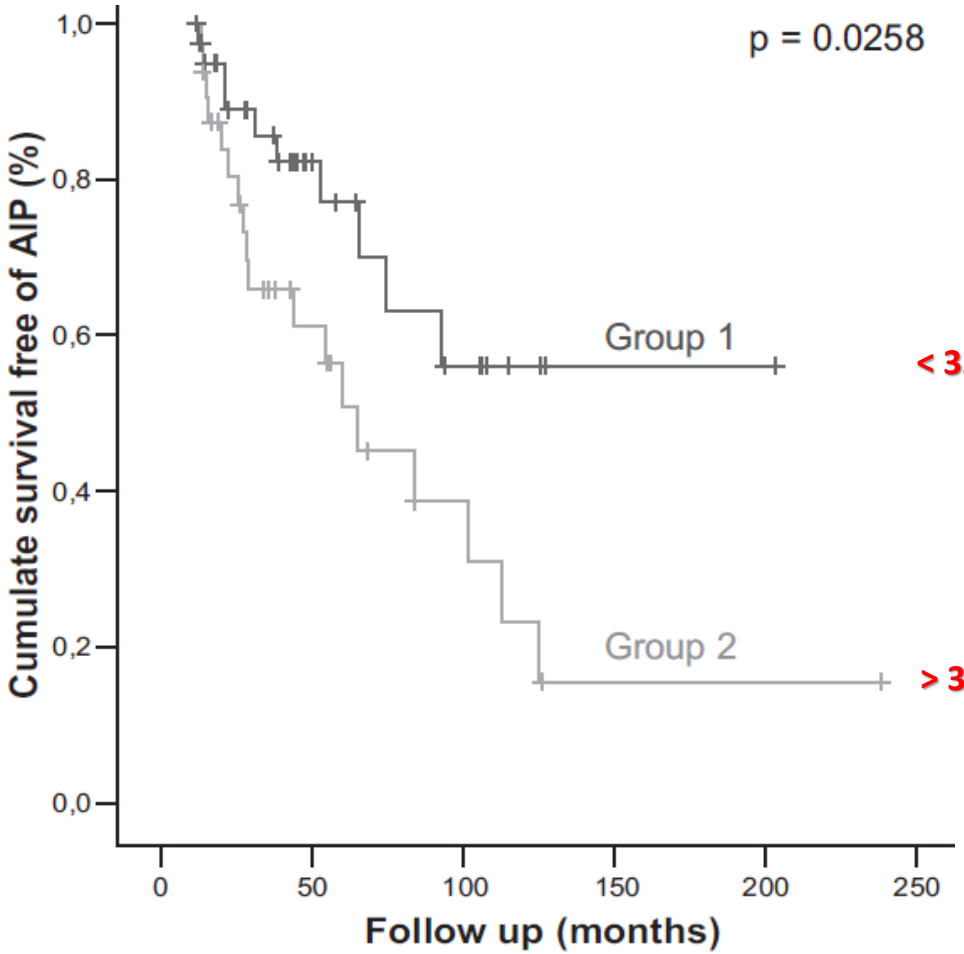
Redefining Clinically Significant Castration Levels in Patients With Prostate Cancer Receiving Continuous Androgen Deprivation Therapy

Juan Morote, Anna Orsola,* Jacques Planas, Enrique Trilla, Carles X. Raventós, Lluís Cecchini and Roberto Catalán

From the Department of Urology, Vall d'Hebron Hospital and Autonoma University of Barcelona School of Medicine, Barcelona, Spain



< 32ng/dl ***PFS:137 months (95% CI 104–170)***

> 32ng/dl ***PFS : 88 months (95% CI 55–121)***

THE JOURNAL OF UROLOGY® Vol. 178, 1290-1295, October 2007

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Milestones

Redefining Clinically Significant Castration Levels in Patients With Prostate Cancer Receiving Continuous Androgen Deprivation Therapy

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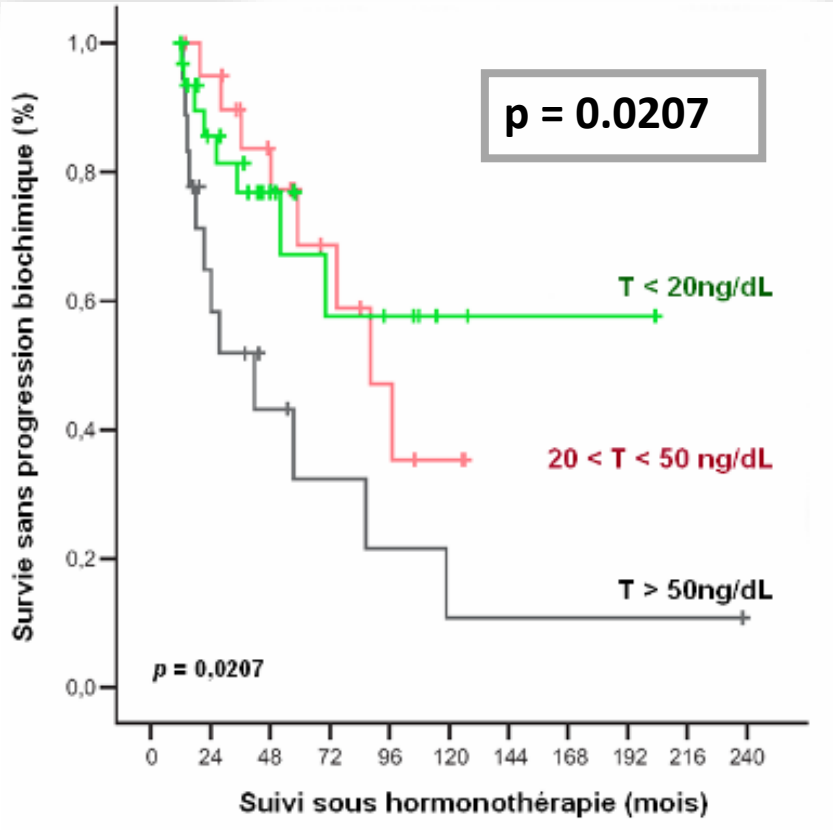
Printed in U.S.A.



106 Months

90 Months

72 Months

Morote *et al.*, *J. Urol* 2007;178:1290-1293

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Milestones

BJUI

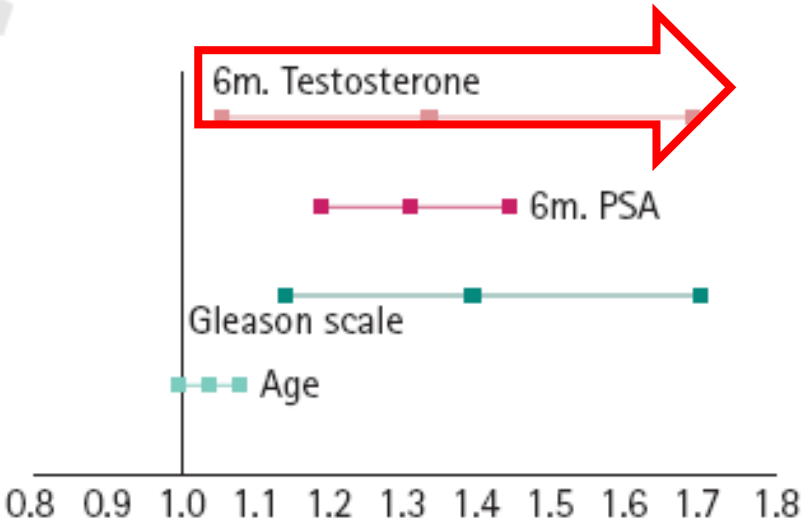
Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone–releasing hormone therapy: prognostic significance?

Massimo Perachino, Valerio Cavalli and Fabio Bravi*

*Department of Urology, Santo Spirito Hospital, Casale Monferrato, Alessandria, and *Department of Biometry, Ibis Informatica s.r.l., Milan, Italy*

Accepted for publication 5 June 2009

FIG. 1. Hazard ratios and related 95% CI.



Statistical analysis using Cox's model showed that in these patients the risk of death was directly correlated to :

-Gleason score (P < 0.01)

-6-months PSA level (P < 0.01)

-6-months serum testosterone level (P < 0.05)

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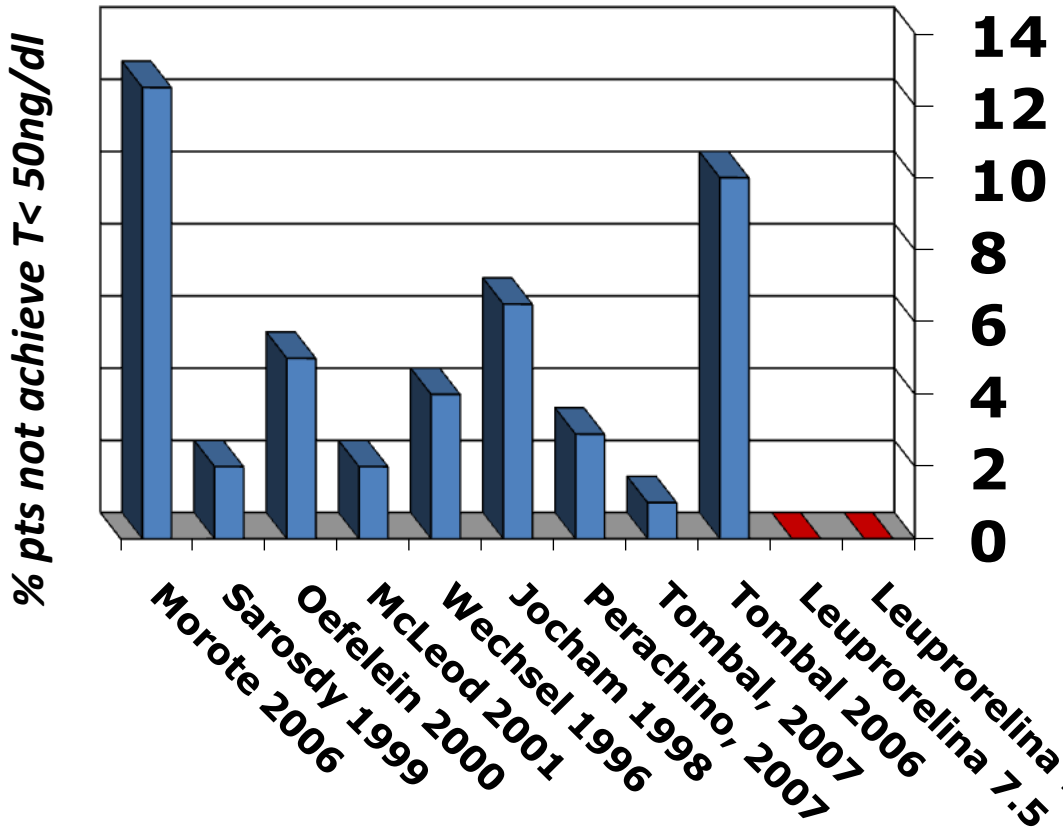
Failure to Achieve T Level to castration



Morote J, et al. Urol Int 2006;77:135; Sarosdy MF, et al. BJU Int 1999;83:801-6; Oefelein MG, et al. J Urol 2000;164:726-9; Wechsel HW, et al. Eur Urol 1996;30(Suppl 1):7-14; McLeod D, et al. Urology 2001;58:756-61; Jocham D, et al. Urol Int 1998;60:18-24. Perachino, EAU 2007, A258, Tombal, EAU 2007, A260

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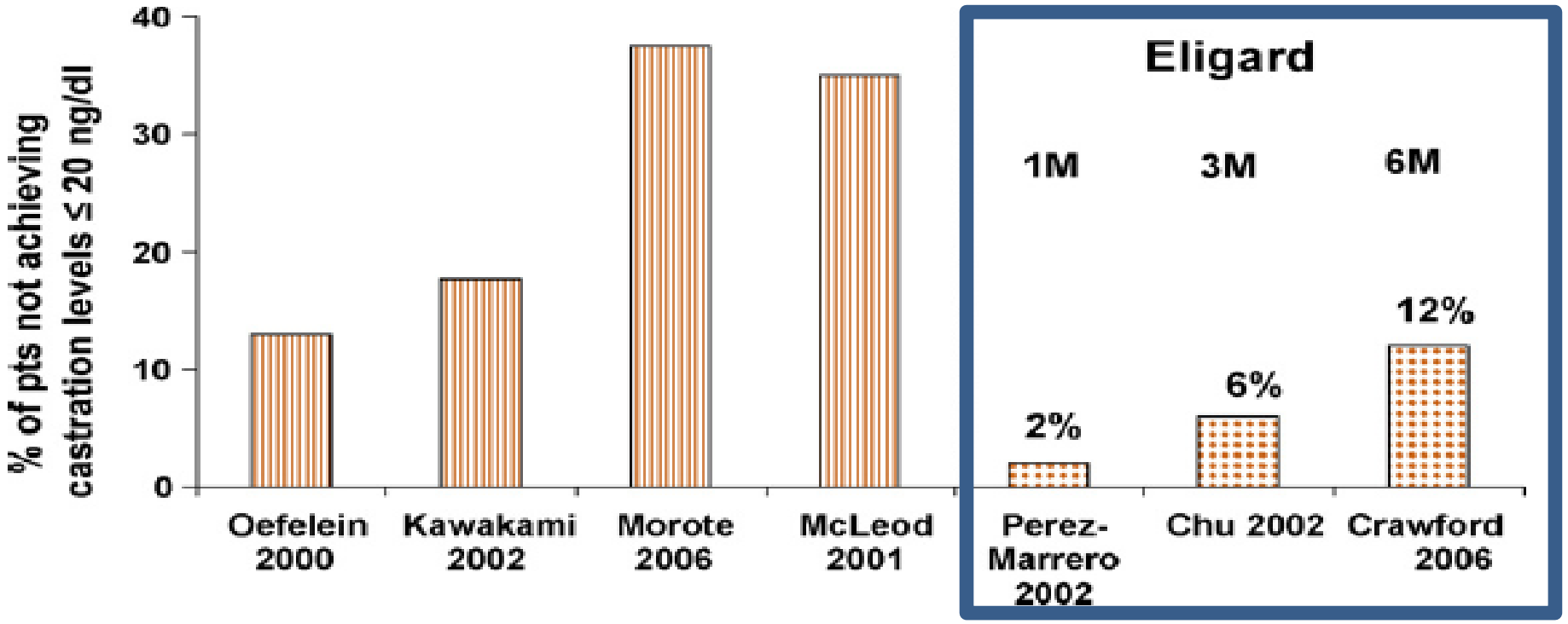
Testosteron Control in PCa



Tombal B- European urology supplements 6 (2007) 834–83

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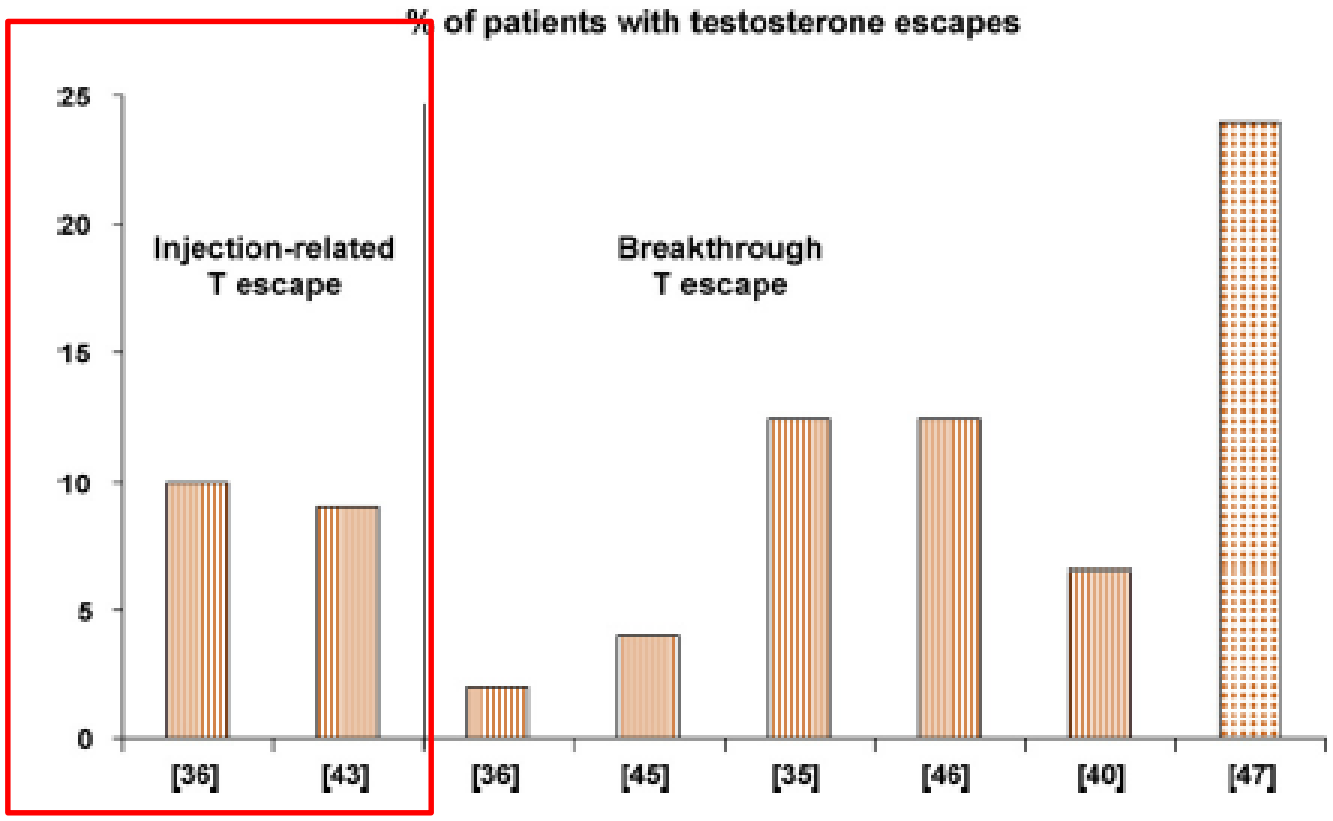
Testosterone escapes

***Miniflares** are defined as rises in testosterone levels 50 ng/dl within 12 h after the second or subsequent injection of the LHRH agonist*



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Pivotal Study of the 6-month SR formulation of Triptorelin

Demographics and Disease characteristics (ITT)

		N =120
Age (years)[a]		71.1 ± 8.5
BMI		
	Normal (≤ 25 kg/m²)	31.7% (n=38)
	Overweight (> 25 kg/m²)	68% (n=81)
Race		
	Caucasian	64.2% (n=77)
	Black	22.5% (n=27)
	Colored (mixed race)	13.3% (n=16)
Duration of prostate cancer (years)		2.8 ± 3.6
TNM stage with incidence ≥ 5%		71.1 ± 8.5
	T3N0MX	5.8% (n=7)
	T3NXMX	45.8% (n=55)
	T4NXM1	5% (n=6)
	T4NXMX	17.5% (n=21)
Increased PSA after failed local therapy		28.3% (n=34)
Serum testosterone (mmol/L)		17.8 ± 7.2
Serum PSA[b] (µg/L)		19.1 (0.1-1630.0)

Lundström EA, et al. *Clin Drug Investig.* 2009; 29:757–765.

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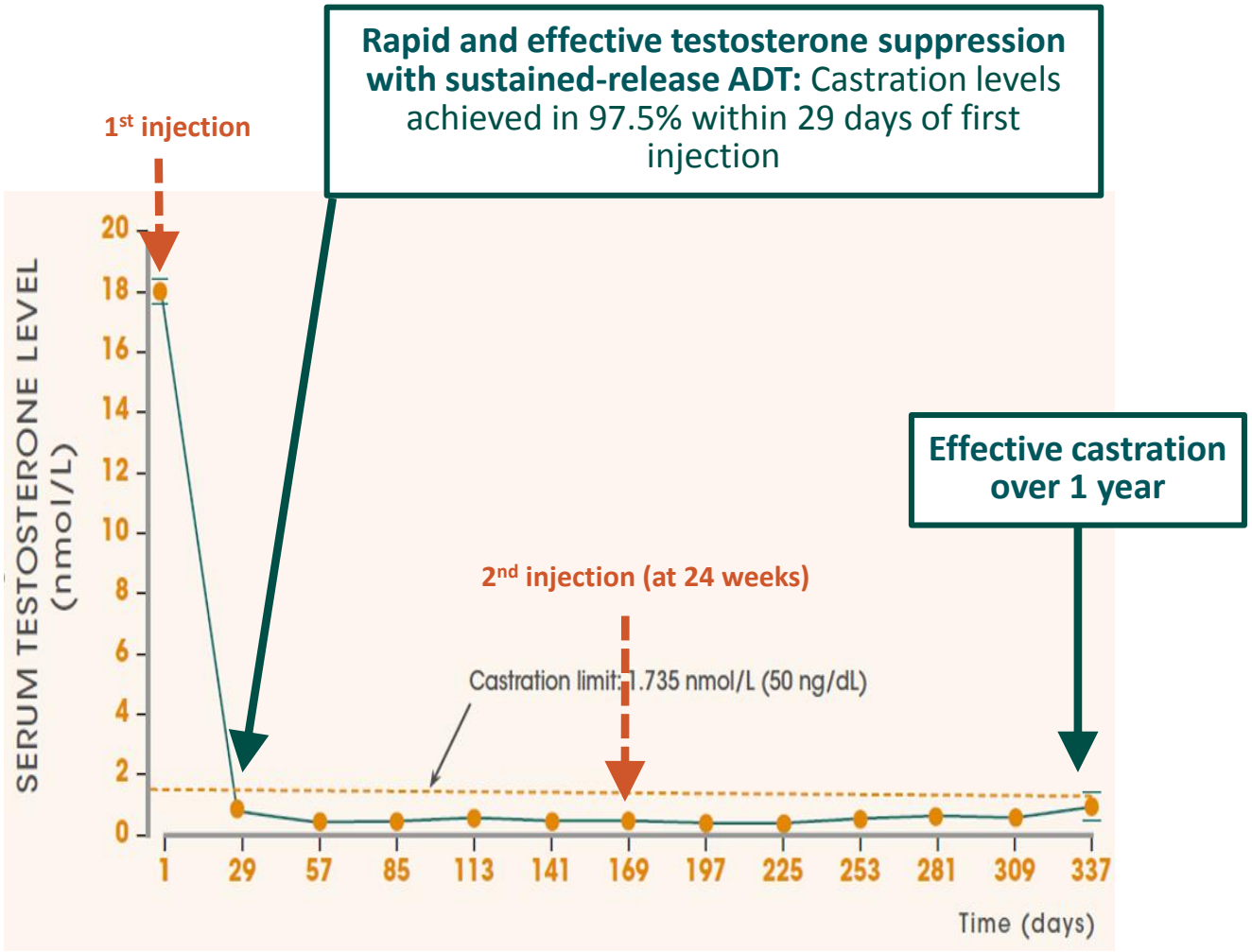
ADT provides consistent testosterone suppression over the long-term

Rapid and effective testosterone suppression with sustained-release ADT: Castration levels achieved in 97.5% within 29 days of first injection



Lundström EA, et al. *Clin Drug Investig.* 2009; 29:757–765.

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Pivotal Study of the 6-month SR formulation of Triptorelin

Primary efficacy results

	Triptorelin 6 Months
Patients castrated at Month 1 (95% CI)	**97.5%** 92.9 - 99.5%
Patients maintaining castration at Month 12 (end of study)	**98.3%** 113/115
Patients maintaining castration (Month 2 to 12)	**93%** 86.8 – 97.0%

97.5% of patients achieved castrate serum testosterone levels by day 29

93% maintained castration from month 2 to month 12 (entire period of the study)

Lundström EA, et al. *Clin Drug Investig.* 2009; 29:757–765.

Adv Ther
DOI 10.1007/s12325-016-0466-7

CrossMark

ORIGINAL RESEARCH

Efficacy of Testosterone Suppression with Sustained-Release Triptorelin in Advanced Prostate Cancer

Jürgen Breul · Eija Lundström · Daniela Purcea · Werner P. Venetz · Patrick Cabri · Pascale Dutailly · Evan R. Goldfischer

Table 2 Demographic data and baseline characteristics, means (range) or *n* (%)

Triptorelin formulation	1 month (3.75 mg)	3 month (11.25 mg)	6 month (22.5 mg)	All
Patients enrolled	489	303	128	920
Age (years)	71.1 (42–96)	70.5 (48–93)	71.1 (51–93)	70.9 (42–96)
Weight (kg)	74.2 (40–129)	74.6 (38–132)	83.3 (47–136)	75.8 (38–136)
BMI (kg/m^2)	24.8 (13–43)	25.2 (16–44)	27.6 (19–42)	25.4 (13–44)
Testosterone (ng/dl)	358.6 (3–1015)	383.1 (40–1296)	502.6 (54–1171)	386.7 (3–1296)
Race[a], *n* (%)	421 (100)	240 (100)	128 (100)	789 (100)
Caucasian	231 (54.9)	147 (61.2)	85 (66.4)	463 (58.7)
Black	128 (30.4)	65 (27.1)	27 (21.1)	220 (27.9)
Coloured	61 (14.5)	27 (11.3)	16 (12.5)	104 (13.2)
Other	1 (0.2)	1 (0.4)	0 (0)	2 (0.2)

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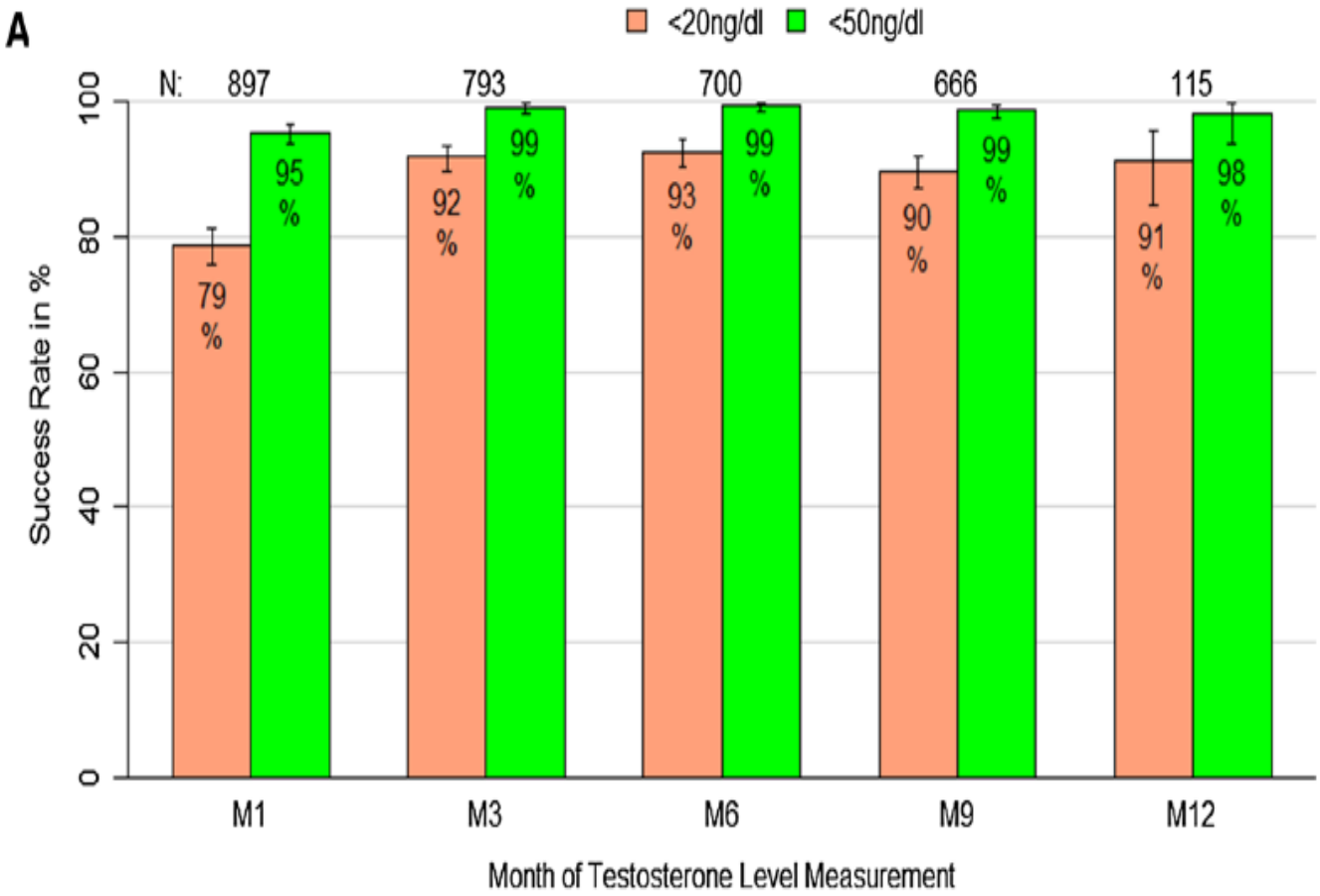
Efficacy of Testosterone Suppression with Sustained-Release Triptorelin in Advanced Prostate Cancer



Retrospective study
Data colleted from
9 prospective studies

- 920 pts
- Treated with 1, 3, 6 mo formulation
- ENDpoint: Testosterone level

The success rates based on the standard castration limit of 50 ng/dl **ranged from 95–99%**

Breul J. et al., Adv Ther 2016

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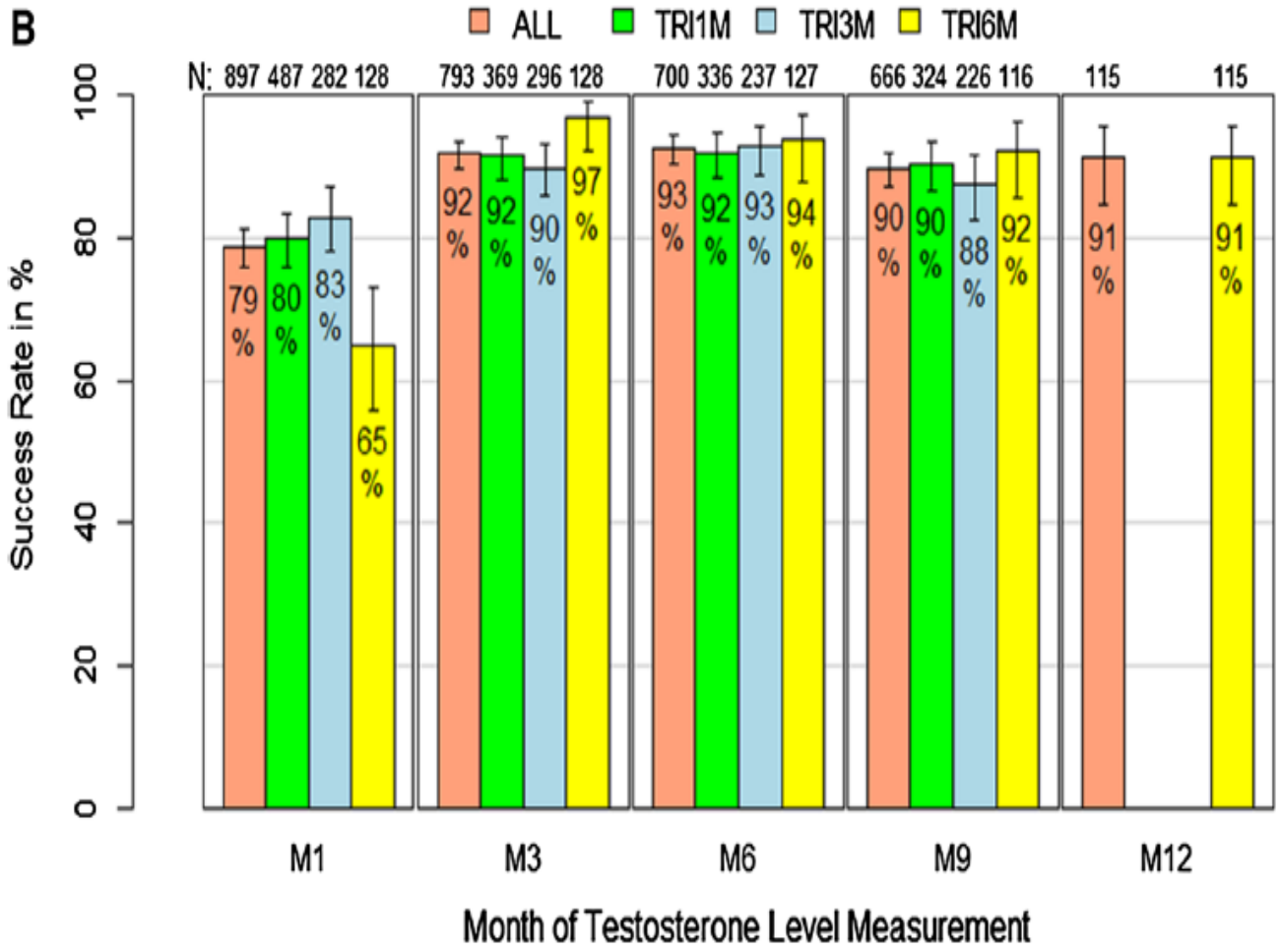
Efficacy of Testosterone Suppression with Sustained-Release Triptorelin in Advanced Prostate Cancer



%T≤ 20ng/dl:

- 80–92% 1-month form.
- 83–93% 3-month form.
- 65–97% 6-monthform.

Breul J. et al., Adv Ther 2016

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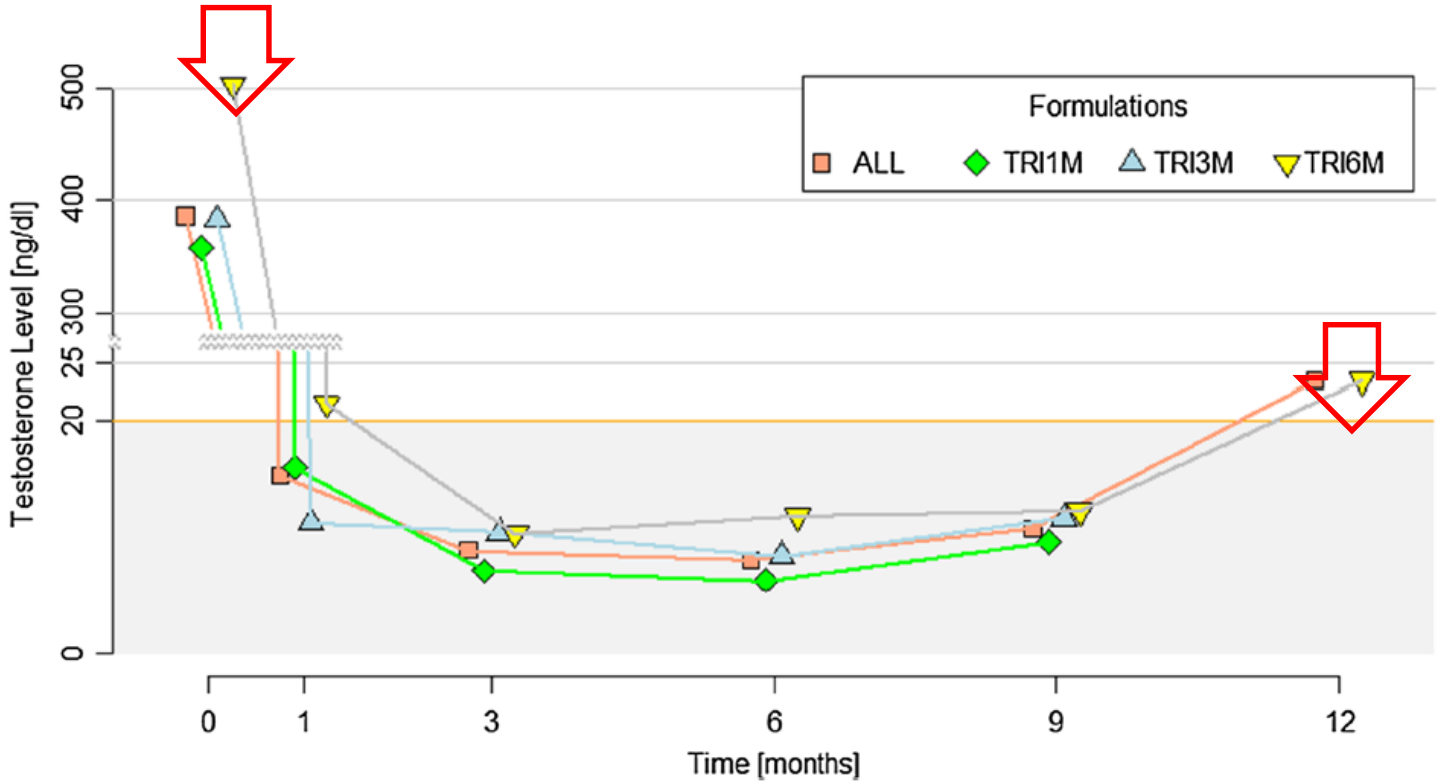
Testosterone Control

Excluding those as outliers would result in mean values of 18.5 and 13.1 ng/dl, respectively.



Breul J. et al., Adv Ther 2016

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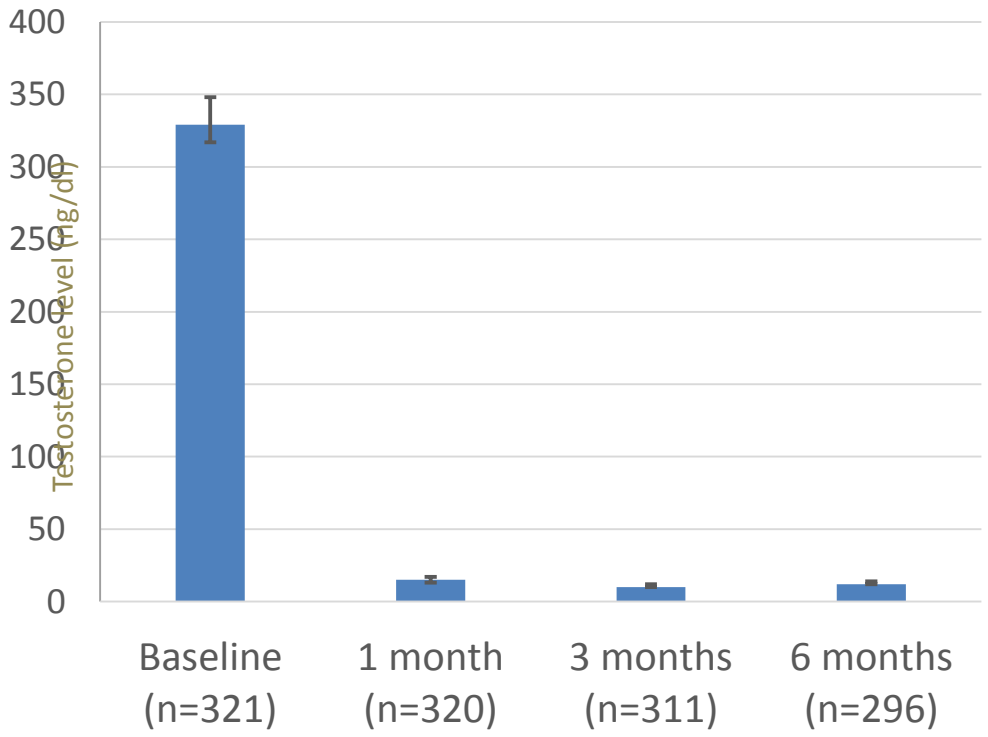
Triptorelin effectively reduces testosterone

Change in testosterone levels from baseline using SR 6-month triptorelin in men with advanced PCa



Triptocare study

- 321 pts
- >90% of patients achieved castrate levels of testosterone (<50 ng/dL) at 1, 3, and 6 months.

Martinez-Pineiro L, et al. *BJU Int.* 2014;114:608–16.

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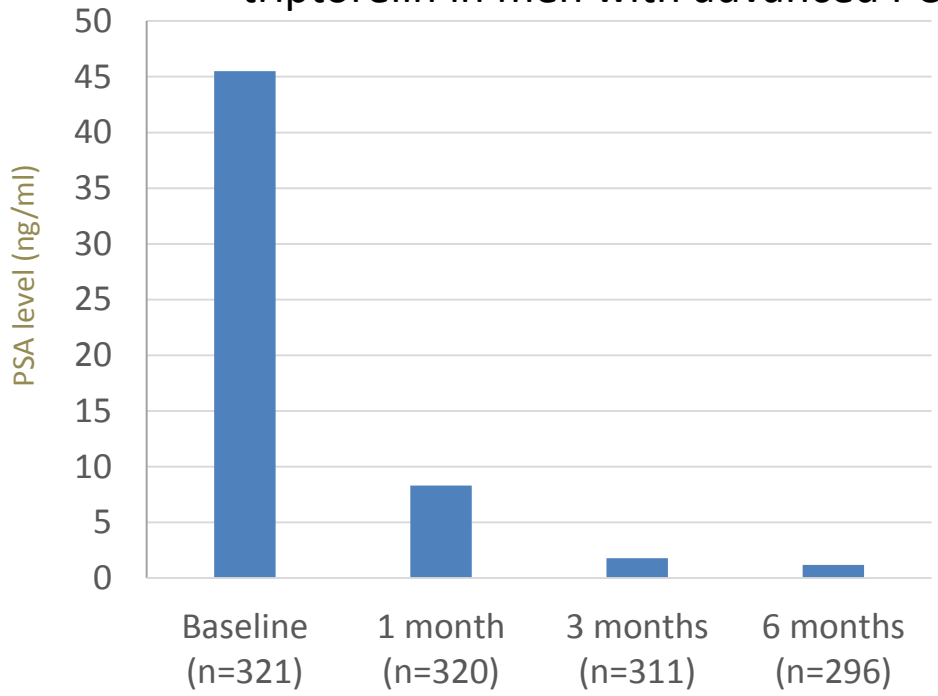
Triptorelin effectively reduces serum PSA

Change in median serum PSA levels from baseline using SR 6-month triptorelin in men with advanced PCa



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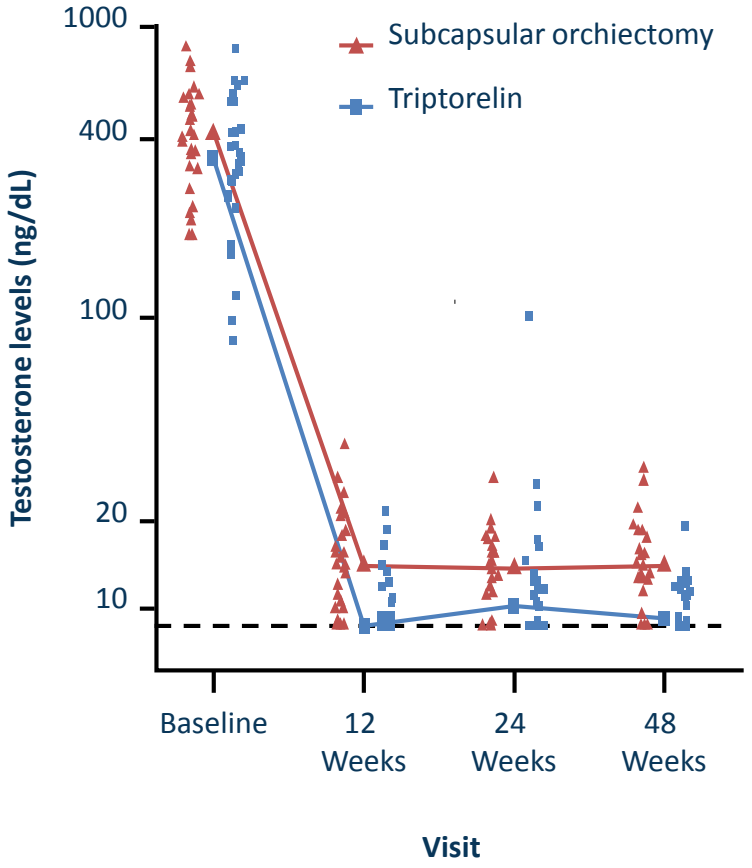
Surgical versus chemical androgen deprivation therapy

Objective: To compare post-treatment androgen levels between men undergoing surgical castration and men treated with a GnRH agonist

Study design

- Open-label, randomised, controlled trial of triptorelin 22.5 mg every 24 weeks and subcapsular orchiectomy (patients randomised 1:1)
- Hormone naive men with prostate cancer and indication for life-long ADT (n=58)
- Follow-up 48 weeks (baseline, 12, 24 and 48 weeks)
- Assay: LCMS

Significantly higher proportion of men receiving triptorelin had testosterone levels <20 ng/dl at 12 and 48 weeks compared with men undergoing orchiectomy (97% vs 79% and 100% vs 87%, respectively, p <0.05).



Østergren PB et al. J Urol. 2017;197(6):1441–1447.

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6-month Side Effects

<u>95.8% of patients experienced an adverse event (AE)</u>

- ***71.7% had hot flushes***
- ***10% had erectile dysfunction***
- ***7,5% had testicular atrophy***

14% had a serious AE (SAE) and 3 deaths were reported (not drug related)

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Local Tollerance

Injection-site reactions 6.7% vs 11.8% and 15.3% of the other available formulations

1-Lundström EA, et al. Clin Drug Investig. 2009; 29:757–765

2-Crawford E. et al. J Urol 2006; 175: 533-6

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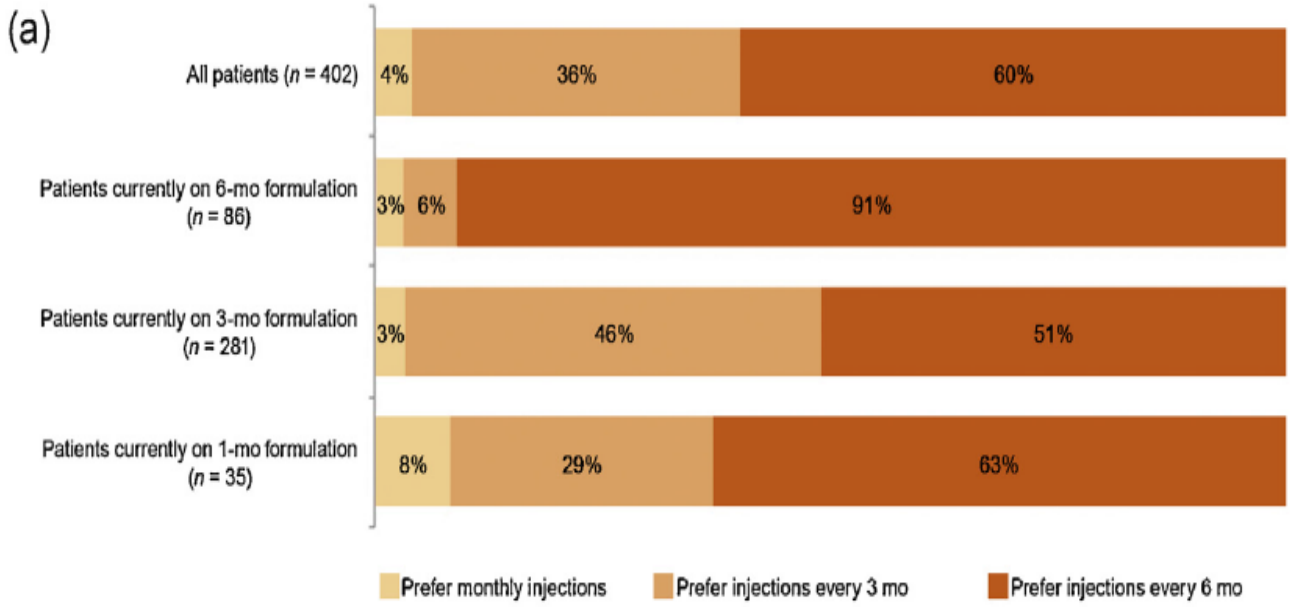
Which Luteinising Hormone-Releasing Hormone Agonist Injection Schedule Do Men with Prostate Cancer Prefer? Results of a European Patient Survey



Patient survey
400 European patients
(Italian N=100)

"Limitations of our study include selection of appropriate and potentially willing participants by physicians, which could have introduced some bias."

Montorsi F. et al.,European Urology 2015

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Triptorelin 6-month formulation: Conclusions

- Efficacious in inducing chemical castration for treatment of advanced prostate cancer
- Comparable efficacy and safety with the marketed 3-month formulation
- This new formulation is more convenient in long-term management of Prostate Cancer.

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