Reinforcing Consistent Testosterone Suppression in ADT:

Avoiding Escapes

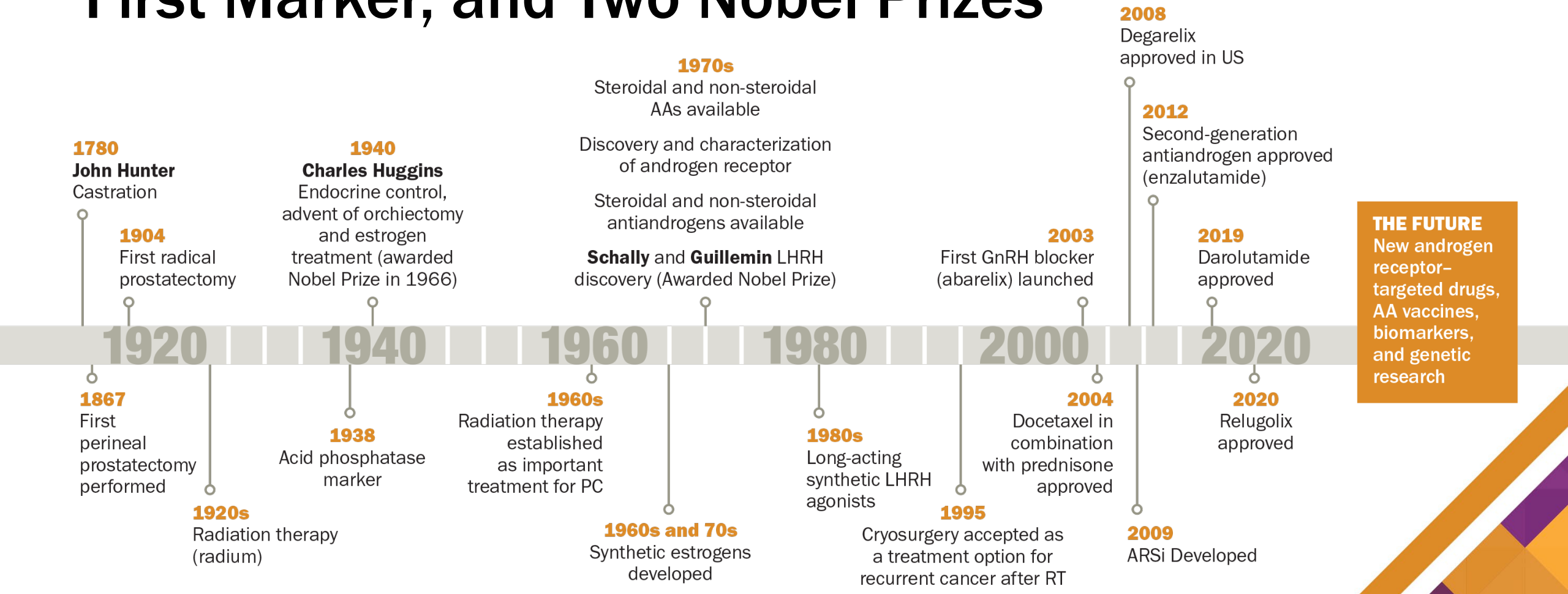
Are All Methods of ADT Similar?

ANSWER

No

- The goal is to lower or block androgens—the lower the better—and keep them as low as possible
- Understand the various strategies to lower or block testosterone

Historical Landmarks: First Effective Treatment, First Marker, and Two Nobel Prizes



ARSi = Androgen Receptor Signaling Inhibitor; AA = antiandrogen; LHRH = luteinizing hormone–releasing hormone; PC = prostate cancer; RT = radiation therapy

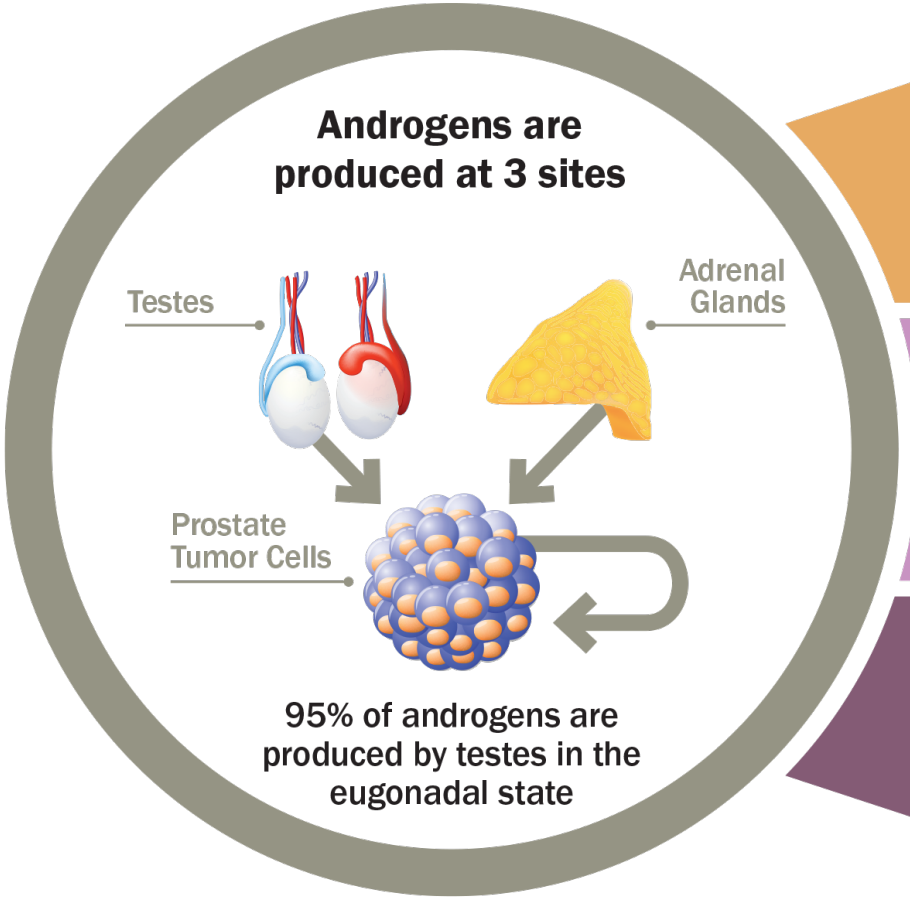
Anderson J. (2009). *Oncology News*: 16–19; McDonnell Mackie Publishing

Hormone Therapy: Current Treatment Options

- Androgen deprivation therapy (ADT)
  - Estrogens
  - Surgical castration (bilateral orchiectomy)
  - LHRH agonists
  - LHRH antagonists
- Antiandrogens
- Combined androgen blockade (CAB)
- 17,20 lyase inhibitors

LHRH = luteinizing hormone-releasing hormone

Androgen Sources

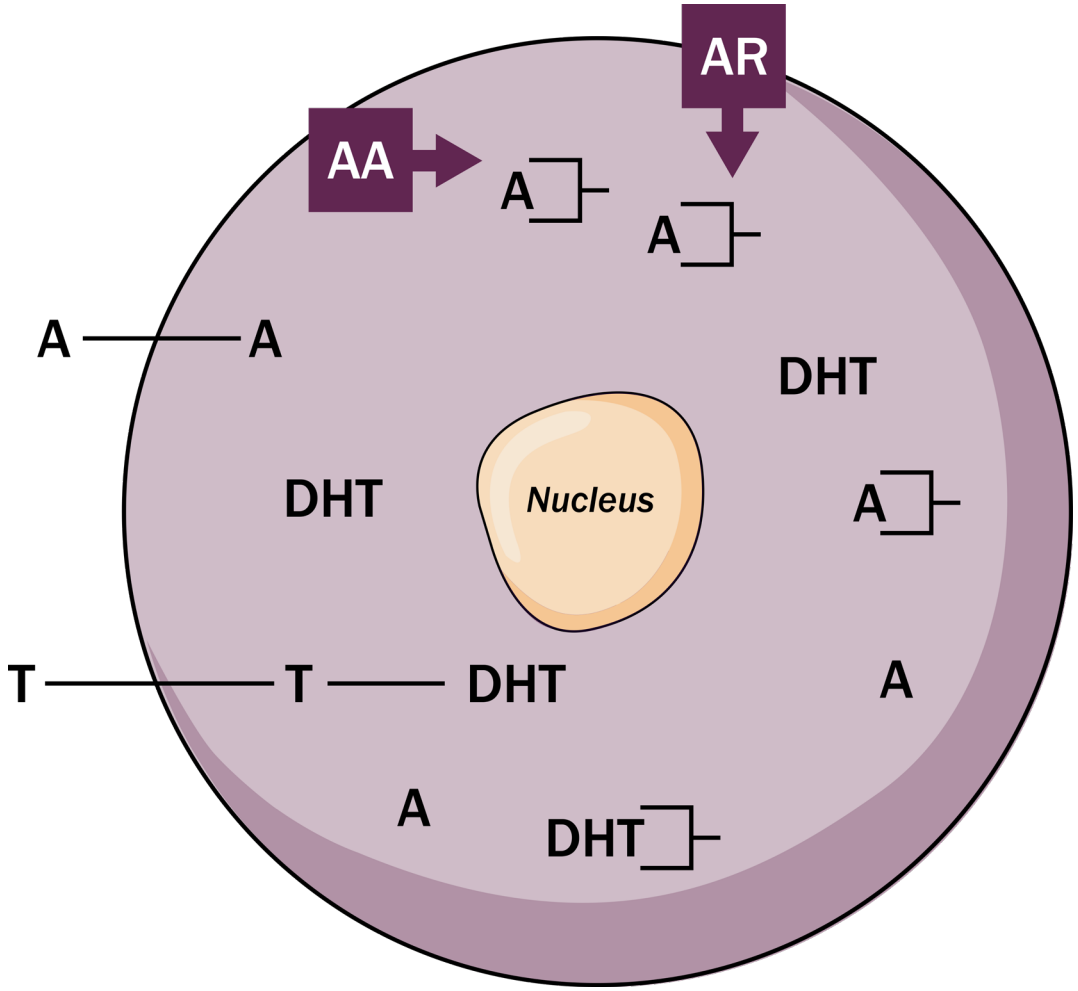


1. Activation of the AR signaling pathway by androgens is **critical** for prostate cancer tumor growth and disease progression
2. Reducing availability of T to bind and activate the AR (lowering T levels or blocking receptor) **decreases** tumor cell proliferation
3. Therefore, targeting the AR by reducing serum T to castrate levels via **ADT** has become standard of care for patients with advanced prostate cancer

ADT = androgen deprivation therapy; AR = androgen receptor

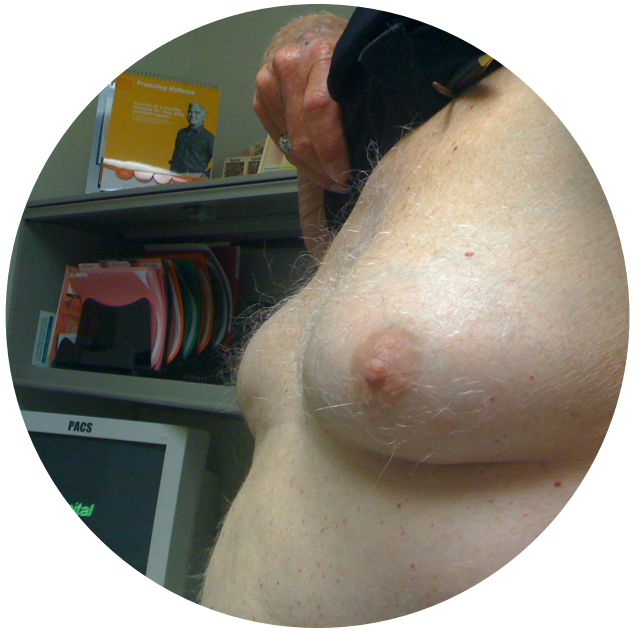
REFERENCES: 1. Sharifi N, et al. *JAMA* 2005;294:238–44. 2005. 2. Scher HI and Sawyers CL. *J Clin Oncol* 2005;23:8253–61. 3. Pomerantz M, et al. In Springer Science + Business Media, LLC; 2009. Ojo D, et al. *Cancers (Basel)* 2015; 7:2290–308. National Cancer Institute. https://www.cancer.gov/types/prostate/prostate-hormone-therapy-fact-sheet. Accessed October 20, 2017.

Antiandrogen Monotherapy



Major Side Effect of AA Monotherapy:

- Gynecomastia



AA = antiandrogen; AR = androgen receptor; DHT = dihydrotestosterone; T = testosterone

ORIGINAL ARTICLE

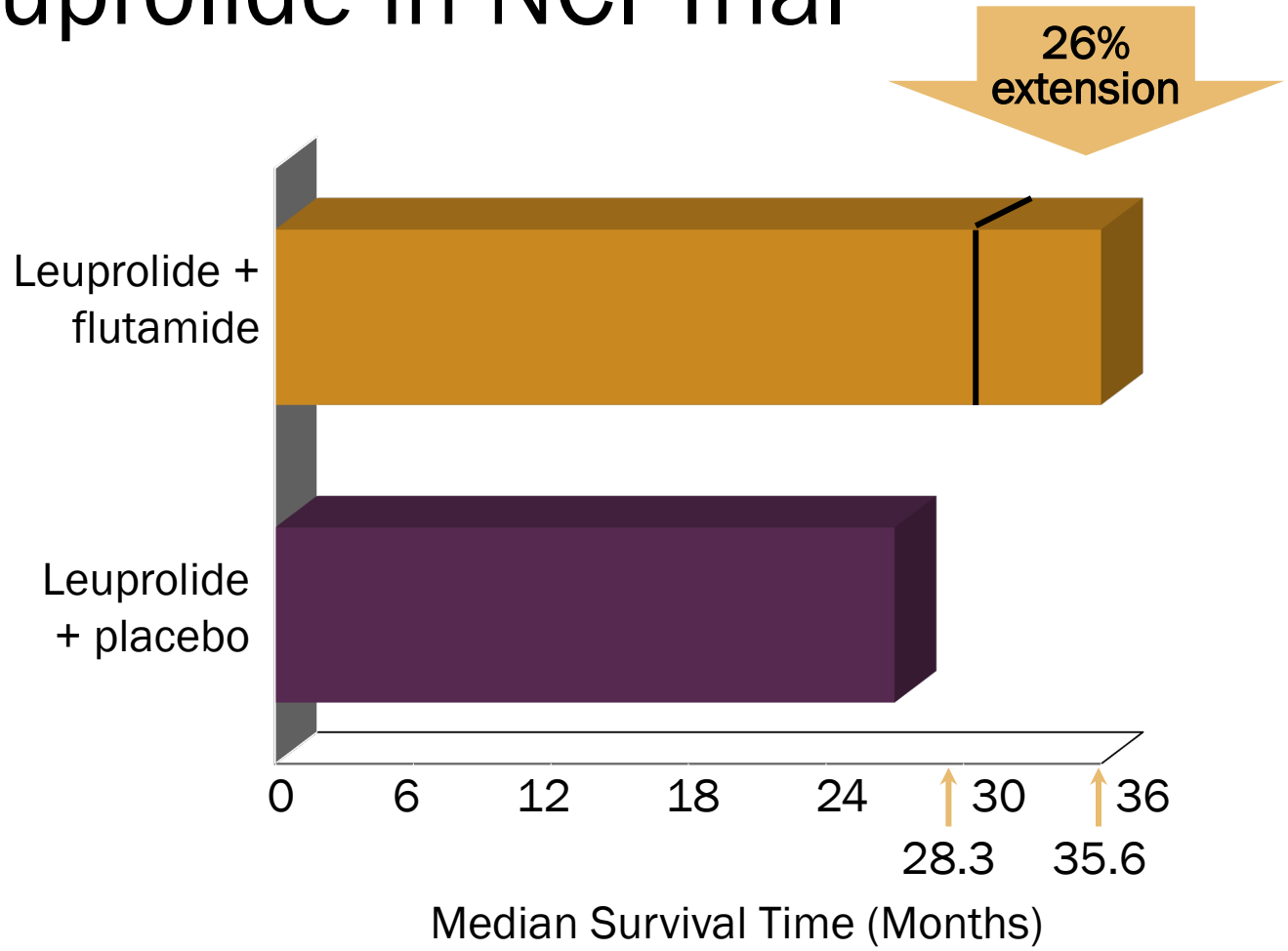
A Controlled Trial of Leuprolide with and without Flutamide in Prostatic Carcinoma

A placebo-controlled randomized trial. A Southwest Oncology Group Study; A National Cancer Institute Intergroup Study

Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, Blumenstein BA, Davis MA, and Goodman PJ

New England Journal of Medicine. 1989;321:419-424; doi: 10.1056/NEJM198908173210702

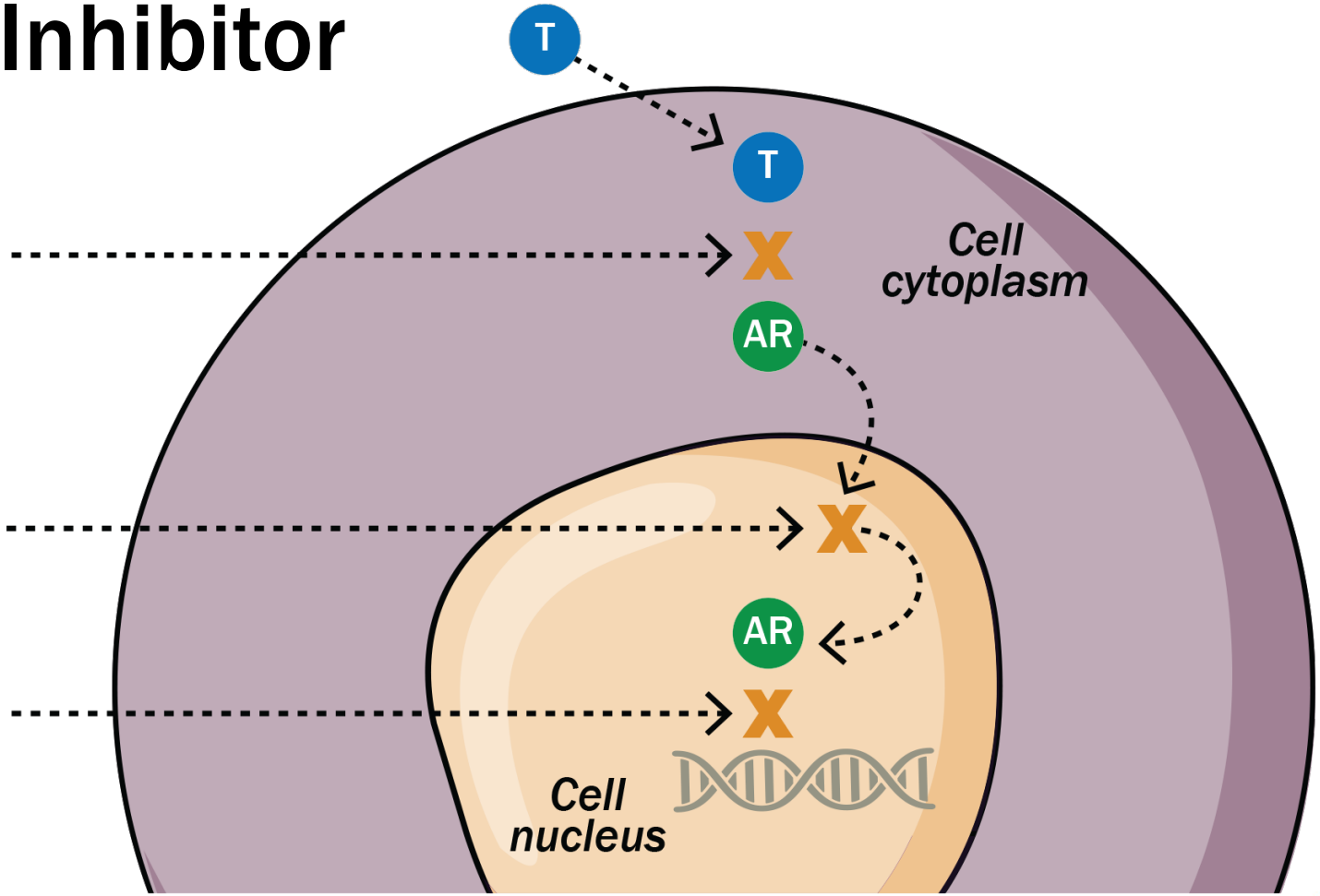
Flutamide Extended Patient Survival in Combination with Leuprolide in NCI Trial



NCI = National Cancer Institute

Enzalutamide: A Third-Generation Androgen Receptor (AR) Inhibitor

1. Inhibits binding of androgens to AR
2. Inhibits AR nuclear translocation
3. Inhibits AR-mediated DNA binding



T = testosterone

Adapted from C Tran et al. *Science*. 2009:787–790

LHRH Analogs 2022

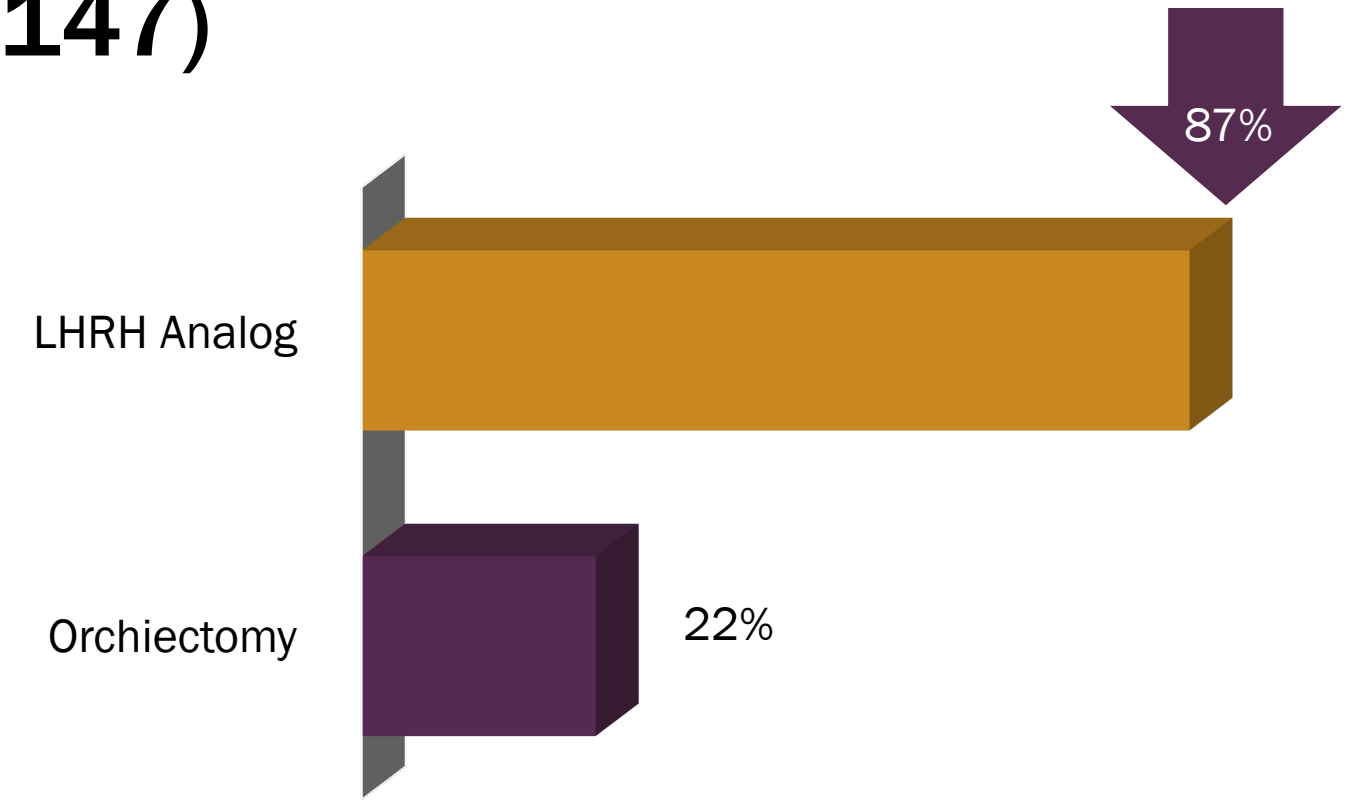
- Daily (subcutaneous)
- Monthly (28 days)
- 3-month depot (84 days)
- 4-month depot (112 days)
- 6-month depot (168 days)
- 12-month depot
- Antagonists (30-day injectable, or daily oral)

LHRH = luteinizing hormone-releasing hormone

Goserelin (Zoladex)

- **Prostatic Carcinoma**
- In controlled studies of patients with advanced prostatic cancer comparing goserelin to orchiectomy, the long-term endocrine responses and objective responses were similar between the two treatment arms. Additionally, duration of survival was similar between the two treatment arms in a comparative trial.
- 292 patients randomized to goserelin versus bilateral orchiectomy and advanced prostate cancer had similar survival rates.

Treatment Choice: LHRH Analog vs. Orchiectomy (*N* = 147)



87% of men preferred LHRH therapy over orchiectomy

LHRH = luteinizing hormone-releasing hormone

Adapted from Cassileth BR et al. *Qual Life Res* 1992;1:323–30

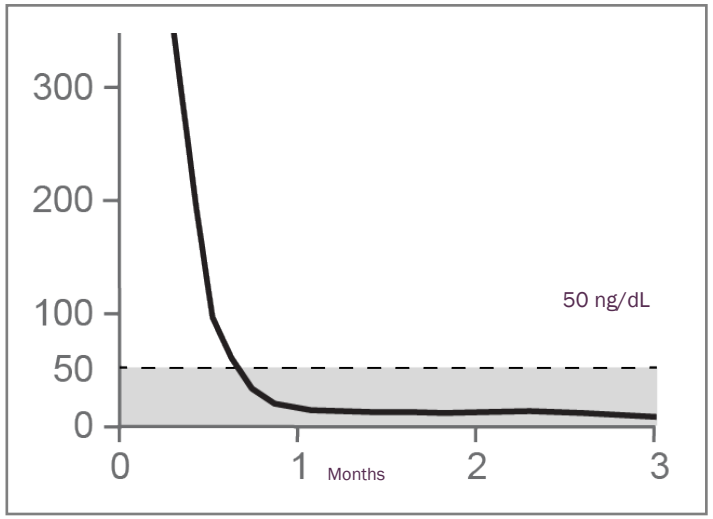
Dr. Andrew Schally

Dr. Andrew Schally, who won the Nobel Prize (physiology or medicine) in 1977, is an endocrinologist conducting research at the University of Miami and U.S. Department of Veterans Affairs.

His discoveries relating to hypothalamic hormones, most notably luteinizing hormone–releasing hormone, have led to the development and approval of many drugs, including drugs for prostate cancer, in vitro fertilization, embryo transfer, and precocious puberty.

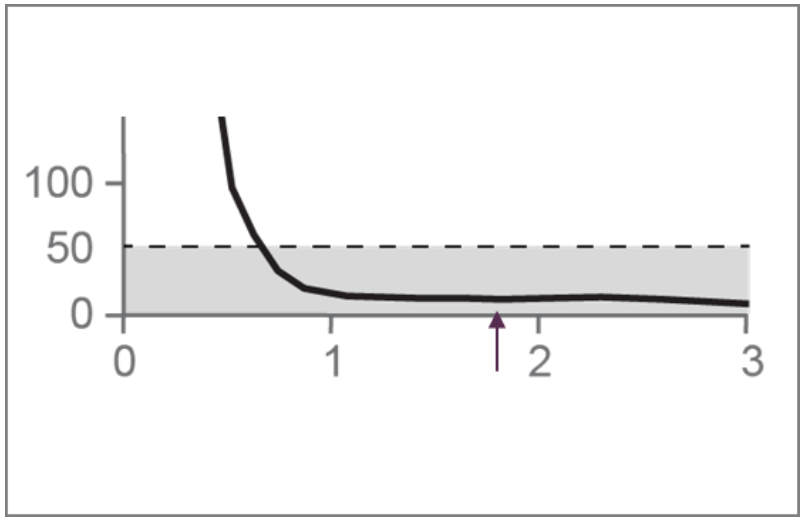
Androgen-targeted Therapy Across the Continuum of Prostate Cancer

Possible Effects of LHRH Therapies on T Profile



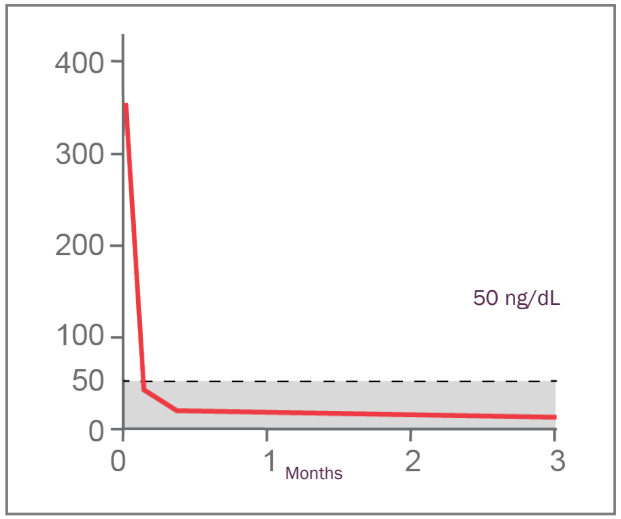
T Suppression Level

Target level of T ≤ 20ng/dL



Nadir T

Lowest level of T measured during therapy



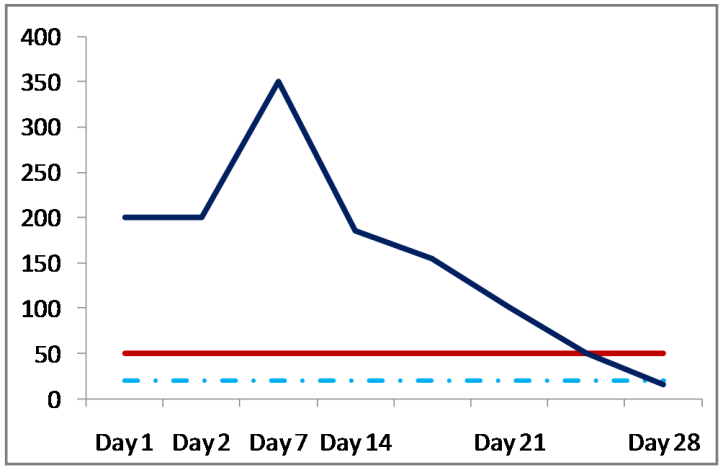
Onset of T Suppression

How quickly castrate T levels achieved.
Antagonist, 2-3 days Agonist, ~3 weeks

Adapted with permission from Crawford ED, et al. 2018 https:doi.org/10.1038/s41391-018-0079-0

Androgen-targeted Therapy Across the Continuum of Prostate Cancer

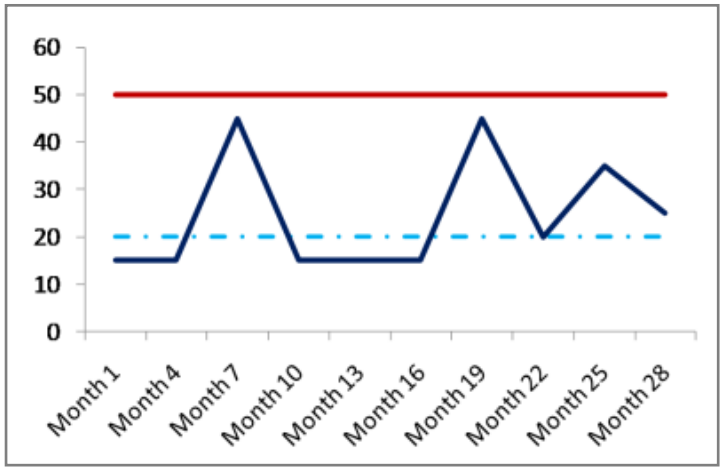
Possible Effects of LHRH Therapies on T Profile



Testosterone Surge/Flare

Surges are T increases >15% for 2 days during first 2 weeks of therapy. Flares are clinical manifestations of surges

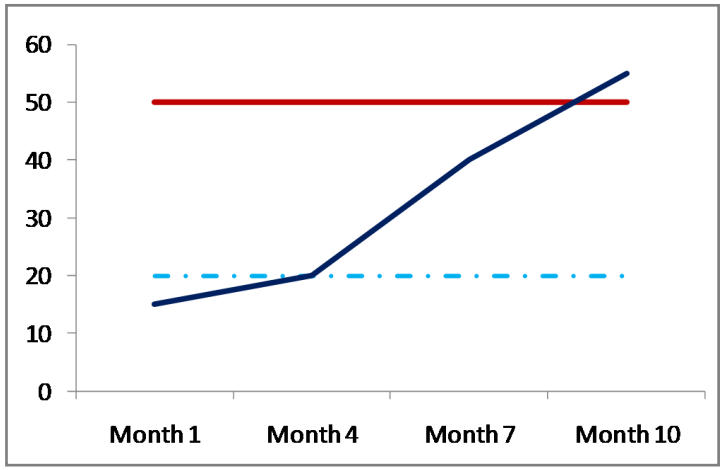
Detrimental: YES



T Microsurges

T increase ≥25 ng/dL within 4 weeks following a subsequent injection of agonist.

Detrimental: LIKELY



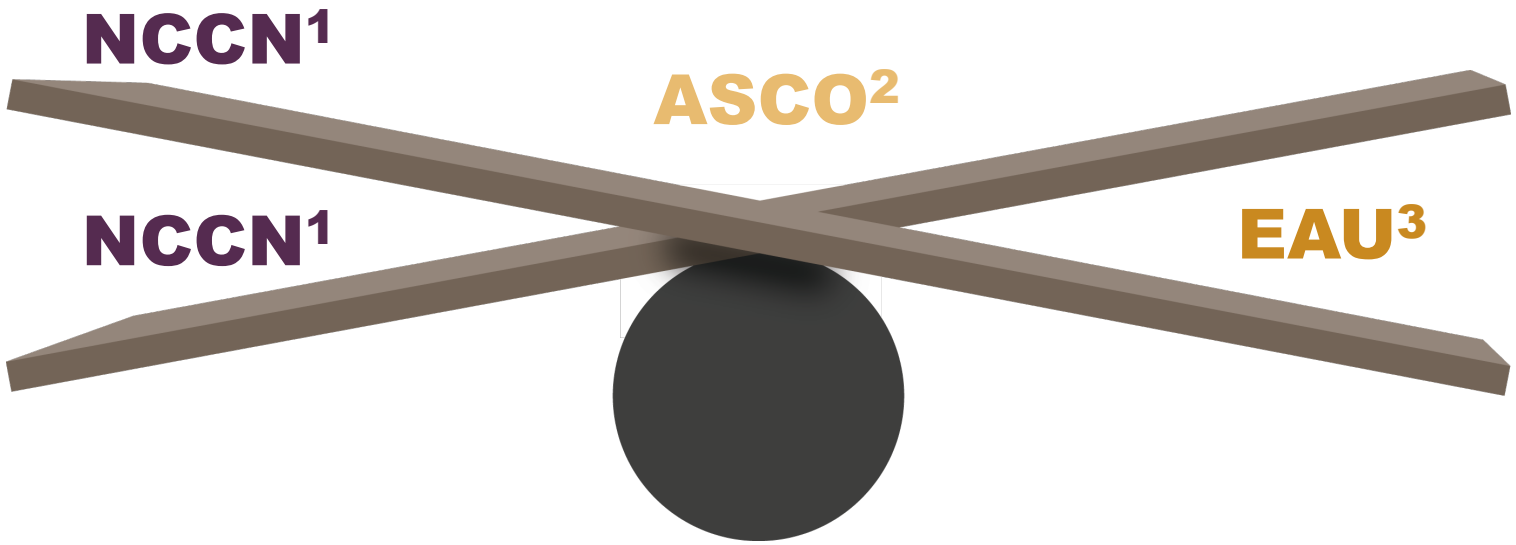
T Escapes

At least one T value >50 ng/dL.

Detrimental: LIKELY

Adapted with permission from Crawford ED, et al. *Prostate Cancer and Prostatic Diseases*. 2018 https:doi.org/10.1038/s41391-018-0079-0

Guidelines on Testosterone Castration Levels



Guidelines Inconsistent Regarding Testosterone Suppression Goal

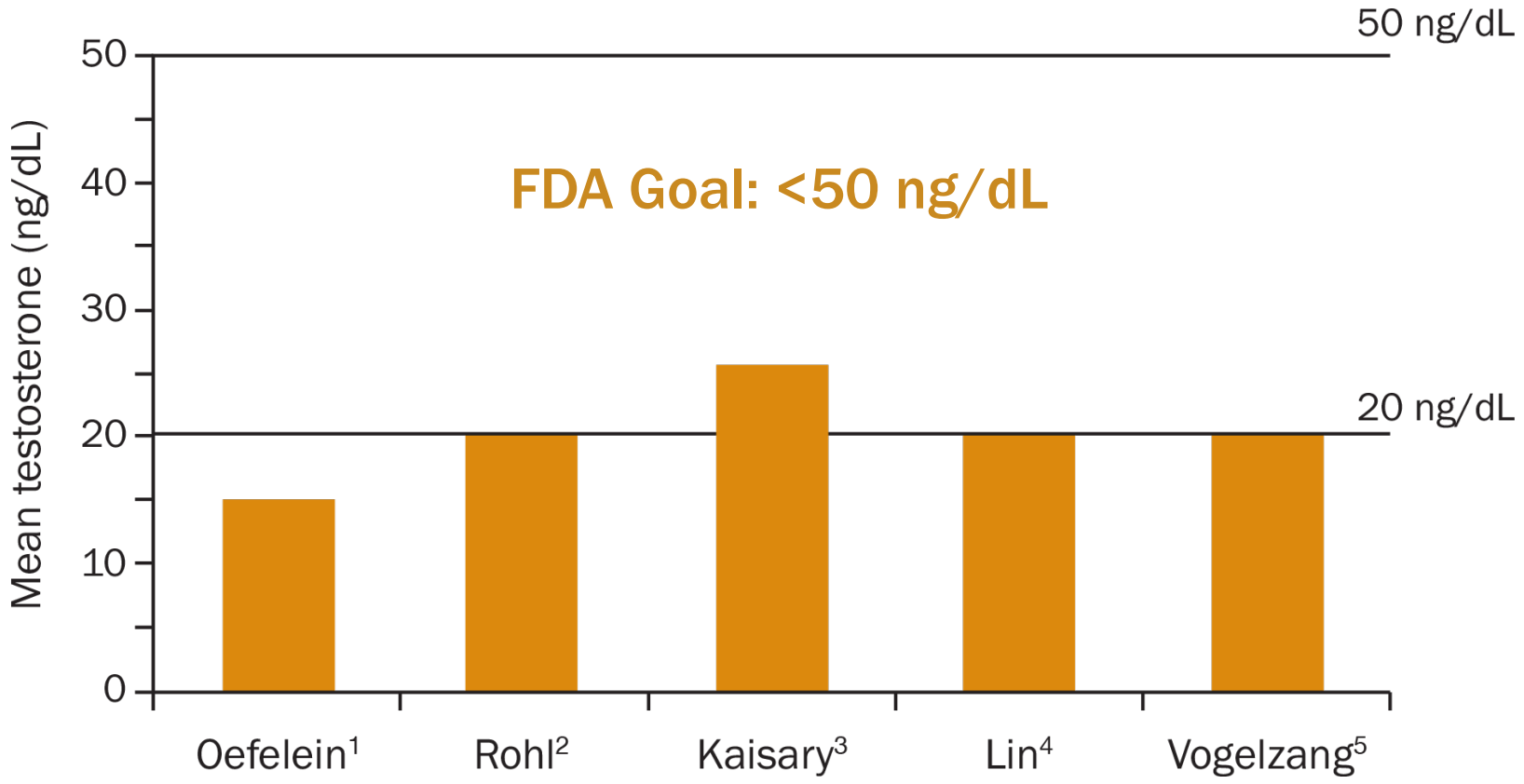
1. National Comprehensive Cancer Network (NCCN). 2020. Clinical Practice Guidelines in Oncology (NCCN Guideline) Prostate Cancer. https://www.nccn.org/patients/guidelines/content/PDF/prostate-advanced-patient.pdf. 2. Loblaw DA et al. *J Clin Oncol*. 2007;25:1596–1605. 3. European Association of Urology (EAU). Guidelines. 2021. http://www.uroweb.org/gls/pdf/09%20Prostate%20Cancer_LRLV2.pdf

Defining Castrate Levels of Testosterone

- Castrate testosterone level traditionally defined as ≤50 ng/dL
- Several investigators have suggested revising the definition of castrate testosterone to ≤20 ng/dL[1-4]
  - Levels after bilateral orchiectomy[2] ≈14 ng/dL
- The rationale:
  - The 50 ng/dL threshold for testosterone level was based on an older, less sensitive technique (double isotope-derivative dilution) that had limited accuracy, especially at the lower limits of detection
  - Using chemiluminescent techniques,[5] sensitivity of testosterone values is as accurate as 0.1 ng/dL (1995)
  - Mass spectrometry,[6] used in some trials, was able to detect testosterone levels <0.1 ng/dL (2003)

1. Røhl HF, et al. *Scand J Urol Nephrol*. 1992;26:11-14;
2. Oefelein MG, et al. *Urology*. 2000;56:1021-1024;
3. Morote J, et al. *J Urol*. 2007;178:1290-1295;
4. Zlotta A, et al. *Eur Urol*. 2005;4(suppl):37-41;
5. Veldhuis JD, et al. *J Clin Endocrinol Metab*. 1995;80:3209-3222;
6. Ongarello S, et al. *Eur Urol*. 2007;6(suppl);150.

How Low Should It Be? The Goal Is <20 ng/dL



1. Oefelein MG et al. *Urology* 2000;56:1021–4
2. Røhl HF, Beuke HP. *Scand J Urol Nephrol* 1992;26:11–43
3. Kaisary AV et al. *Br J Urol* 1991;67:502–8
4. Lin BJ et al. *Urology* 1994;43:834–7
5. Vogelzang NJ et al. *Urology* 1995;46:220–6

Figure taken from:
Tombal B, Berges R. *Eur Urol Suppl* 2005;4:30–6

Do T Escapes and Levels Really Matter?

ANSWER

Yes

Mounting Evidence Supporting a New Castration Definition of <20 ng/dL

Morote J et al. J Urol
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, Roberto Catalán

Perachino M et al. B J U Int.
Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone-releasing hormone therapy: prognostic significance?

Massimo Perachino, Valerio Cavalli, Fabio Bravi

Bertaglia et al. Clin Genitourinary Cancer
Effects of serum testosterone levels after 6 months of androgen deprivation therapy on the outcome of patients with prostate cancer

Valentina Bertaglia, Marcello Tucci, Cristian Fiori, Emiliano Aroasio, Massimiliano Poggio, Consuelo Buttigliero, Susanna Grande, Andrea Saini, Francesco Porpiglia, Alfredo Berruti

2007 2008 2009 2010 2011 2012 2013 2014 2015

Perachino M et al. J Urol.
Testosterone (T) level correlates with survival in pts with advanced prostate cancer (APC): The lower is really the better

Massimo Perachino and Valerio Cavalli

Dason et al. Can Urol Assoc J.
Defining a new testosterone threshold for medical castration: Results from a prospective cohort series

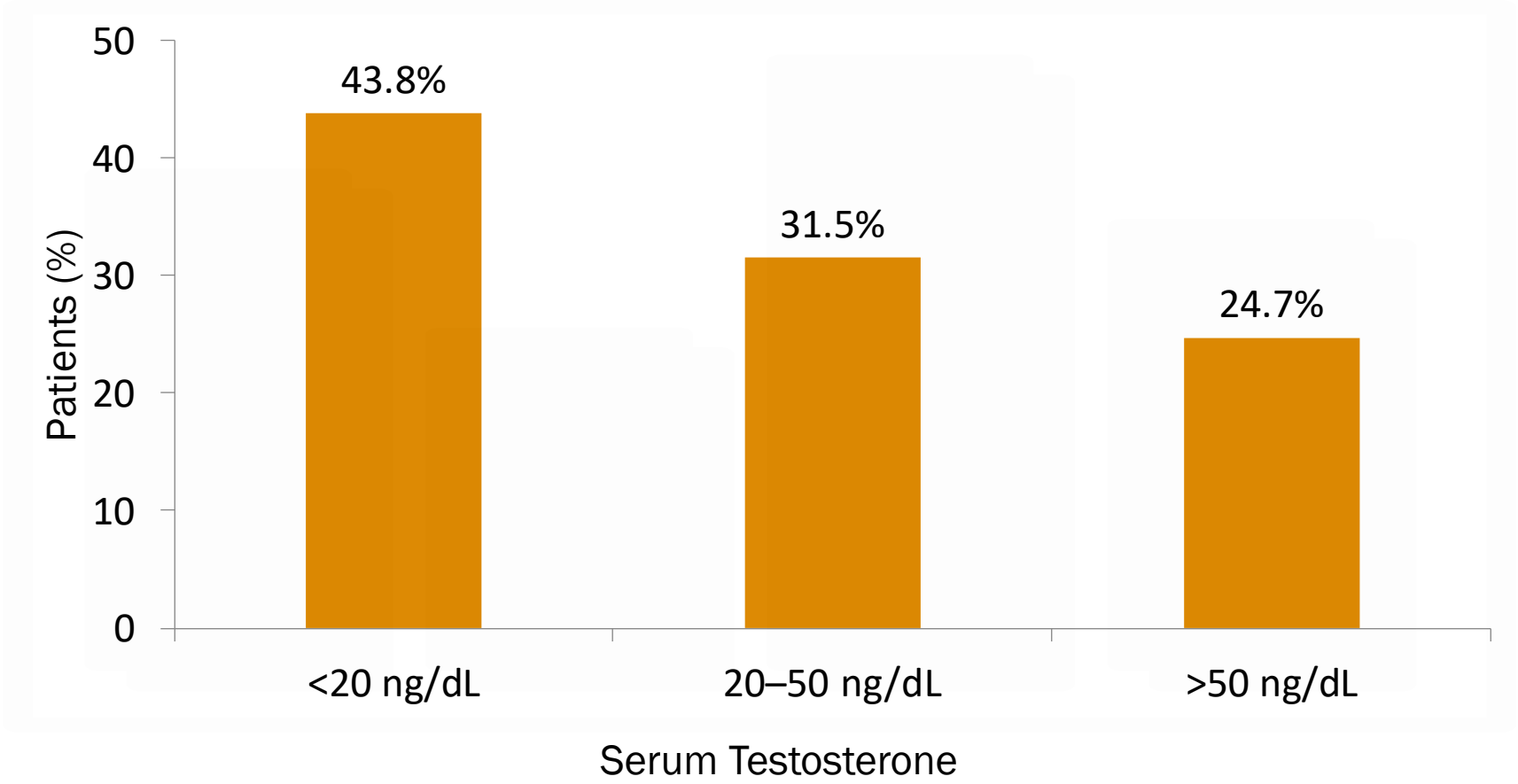
Shawn Dason, Christopher B Allard, Justin Tong, Bobby Shayegan

Klotz et al. J Clin Oncol.

Drs. Morote, Crawford, and Perachino

Juan Morote, MD, PhD;
E. David Crawford, MD;
Massimo Perachino, MD

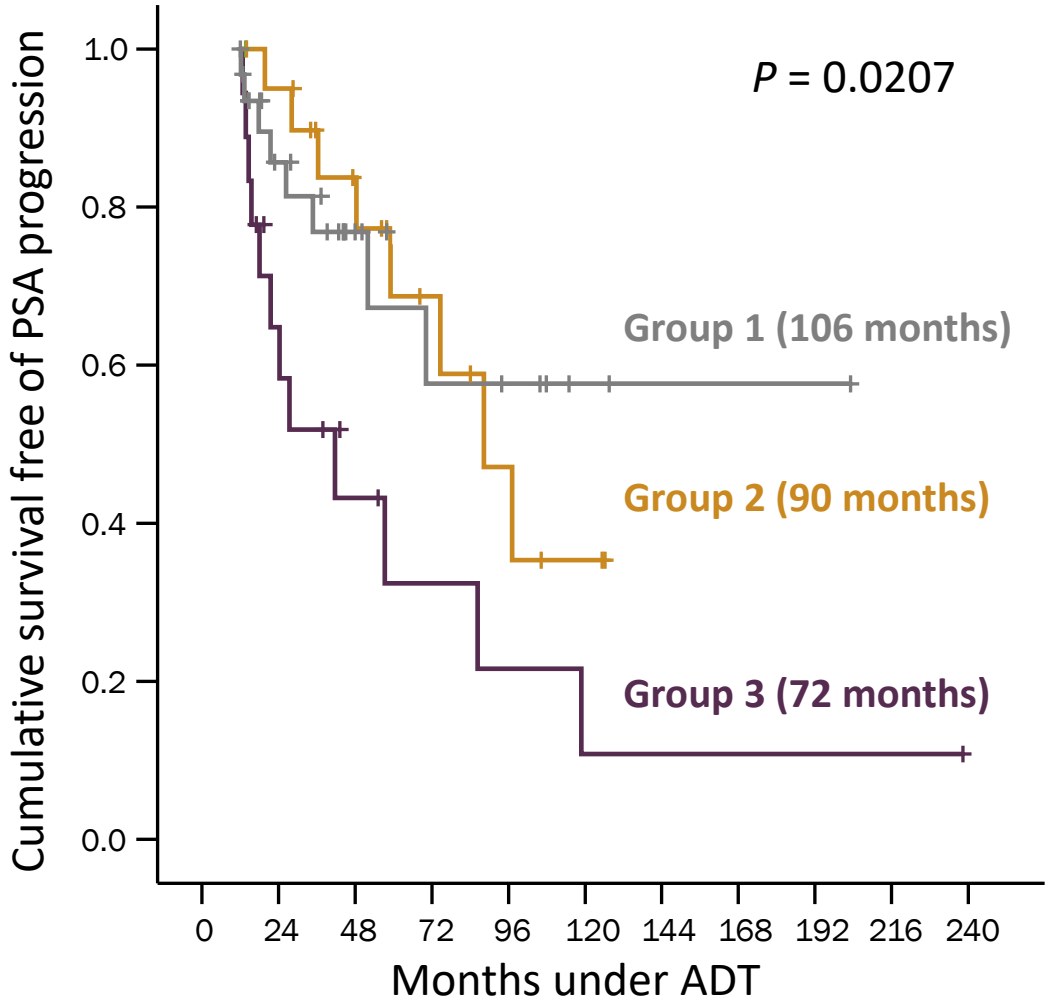
Testosterone Escapes Occur Frequently During LHRH Agonist Therapy



LHRH = luteinizing hormone-releasing hormone

Adapted from Morote J et al. *J Urol* 2007;178:1290–5

Survival Free of AIP According to Serum Testosterone Behavior



Testosterone increases

Group 1: <20 ng/dL

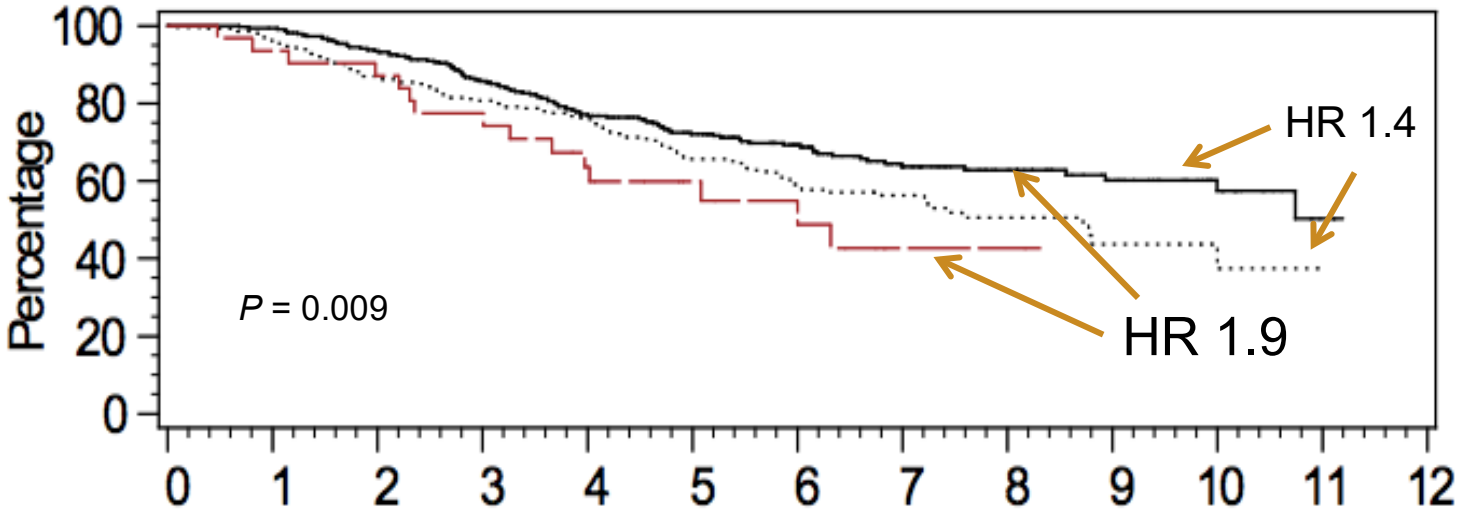
Group 2: 20–50 ng/dL

Group 3: >50 ng/dL

ADT = androgen deprivation therapy; AIP = androgen-independent progression; PSA = prostate-specific antigen

Adapted from Morote J et al. *J Urol* 2007;178:1290–5

PR7 and Survival Based on T Levels



Testosterone increase (ng/dL)	No. at risk												
<20	330	326	298	256	218	174	128	87	63	42	21	4	0
20-50	265	252	223	204	184	135	92	56	31	19	6	1	0
>50	31	29	27	24	17	12	9	2	2	0	0	0	0

HR = hazard ratio; PR7 = randomized controlled trial by the National Cancer Institute of Canada; T = testosterone

Comparison Chart of Six Studies

Primary Author	Year	# of Patients	Retrospective/ Prospective	Delay Disease	Improve Survival	Castration Threshold (ng/dL)	HR For Death*
Morote	2007	73	Retrospective	✓	✓	<20	2.8
Perachino	2008	162	Retrospective		✓	<20	1.92
Perachino	2010	129	Retrospective		✓	n/a	1.32
Dason	2013	32	Prospective	✓		<32	n/a
Bertaglia	2013	153	Prospective	✓	✓	<30	0.45**
Klotz	2015	626	Prospective		✓	<20	2.8

HR = hazard ratio; n/a = not available; *HR for death in patients above castration threshold; **HR for death in patients below castration threshold

Morote J, et al. *J Urol*. 2007;178:1290-1295; Perachino M, et al. unpublished; Perachino M, et al. *BJU Int* 2010;105:648–651; Dason S, et al. *Can Urol Assoc J* 2013;7:e263–e1267; Bertaglia V, et al. *Clin Genitourin Cancer* 2013;11:325–330.e1; Klotz L. *Grand Rounds in Urology*: Minimizing morbidity and maximizing outcomes with ADT. April 15, 2018. https://grandroundsinurology.com/minimizing-morbidity-and-maximizing-outcomes-with-adt/.

Lower Testosterone Delays Time to CRPC and Mortality

Morote et al. 2007	Perachino et al. 2010	Bertaglia et al.2013	Dason et al. 2013	Klotz et al. 2014
• *n* = 73 • Retrospective • Nonmetastatic PrC • Mean follow-up 51 mo. • T <20 ng/dL: 32 patients • T 20–50 ng/dL 23 patients • T >50 ng/dL: 18 patients	• *n* = 129 • Retrospective • Bone metastasis • Mean follow-up 47.5-mo. • At analysis, 58 alive 71 dead	• *n* = 153 • Prospective • 54 metastatic and 99 biochemical failure • Median follow-up 65 mo. Using ROC 30 ng/dL T cutoff	• *n* = 32 • Prospective • Consecutive patients on ADT with T <50 ng/dL • Mean follow-up 26 mo.	• *n* = 626 • Prospective (PR7 continuous arm) • T assayed every 2 mo (minimum 3x in 1st year) • Median follow-up 8 yr • 226 developed CRPC
AIP T < 32 ng/dL: 137 mo. T > 32 ng/dL: 88 mo.	**CSS** Men with higher T at 6 mo had 33% increase in risk of death from cancer, HR 1.33 (95% CI 1.05–1.69, *P* < 0.05)	**OS** T <30 ng/dL at 6 months had 55% decreased risk of death HR 0.45 (95% CI 0.22–0.94, *P* = 0.034)	**CRPC** T <32 ng/dL: 33.1 mo. T 32–50 ng/dL: 12.5 mo.	**CRPC** T <0.7 nmol/L: HR 1.0 T 0.7-1.7nmol/L: HR 1.40 T > 1.7 nmol/L: HR 2.32 **CSS** T <0.7 nmol/L: HR 1.0 T 0.7-1.7nmol/L: HR 1.84 T >1.7 nmol/L: HR 2.61

113 Canadian Urologists surveyed (Shayegan et al. 2012)

- **Only 24% of urologists measure testosterone routinely**
- **Over half (53%) considered testosterone <50 ng/dL to be an adequate castration level**

10 American urologists surveyed (Verity Ad Board 2020)

- **10% of urologists measure testosterone routinely**

ADT = androgen deprivation therapy; AIP = androgen-independent progression; CI = confidence interval; CRPC = castrate-resistant prostate cancer; CSS = cancer-specific survival; HR = hazard ratio; OS = overall survival; PrC = prostate cancer; ROC = receiver operating characteristic; T = testosterone

Morote J, et al. *J Urol*. 2007;178:1290-1295; Perachino M, et al. *BJU Int* 2010;105:648–651; Dason S, et al. *Can Urol Assoc J* 2013;7:e263–e1267; Bertaglia V, et al. *Clin Genitourin Cancer* 2013;11:325–330.e1; Klotz L. *Grand Rounds in Urology*: Minimizing morbidity and maximizing outcomes with ADT. April 15, 2018. https://grandroundsinurology.com/minimizing-morbidity-and-maximizing-outcomes-with-adt/.

ORIGINAL ARTICLE

The Impact of Late Luteinizing Hormone-Releasing Hormone Agonist Dosing on Testosterone Suppression in Patients with Prostate Cancer: An Analysis of United States Clinical Data

E David Crawford,*,† Przemyslaw W Twardowski, Raoul S Concepcion, Jason M Hafron, Richard G Harris, Judd W Moul, Lucio N Gordan, Daniel P Petrylak, Stuart N Atkinson, Deborah M Boldt-Houle, Thomas E Keane, Celestia S Higano, R Jonathan Henderson, A Karim Kader, Maha H Hussain, Neal D Shore

Objectives of study included:

- evaluation of timeliness of ADT dosing
- impact of non-adherence on T levels
- frequency of T and PSA testing in patients with prostate cancer

ADT = androgen deprivation therapy; PCa = prostate cancer; PSA = prostate-specific antigen; T = testosterone

SOURCE: Crawford E.D. et al.,*The Journal of Urology*. Vol. 203, 743-750, April 2020.

Frequency of PSA and T Testing

83% of injections were associated with a PSA test

13% were associated with a T test

PSA = prostate-specific antigen; T = testosterone

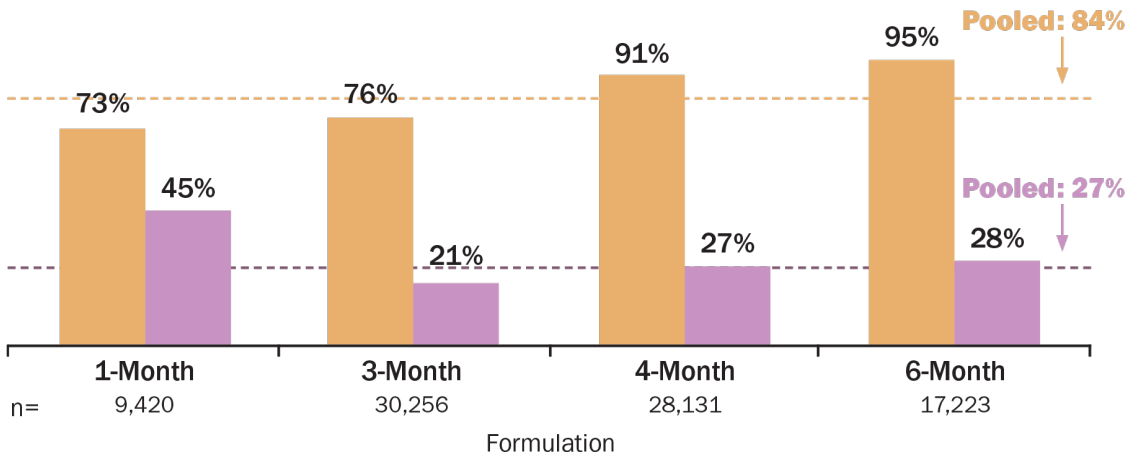
Results

Proportions of late dosing: 84% of dosing occurred later than schedules used in pivotal trials

28-day Month
On average, 84% of injections were late

Extended Month
On average, 27% of injections were late

Proportion of LHRH agonist injections administered late, pooled and by formulation



28 DAY MONTH	
>1 Week	>2 Weeks
60%	29%

LATE	
>1 Week	>2 Weeks
13%	9%

Impact of dose timing on mean T levels:

- Early/on-time dosing: mean T level 21 ng/dl for both definitions
- Late dosing: **mean T levels of 49 ng/dl for 28-day Month and 79 ng/dl for Extended Month**

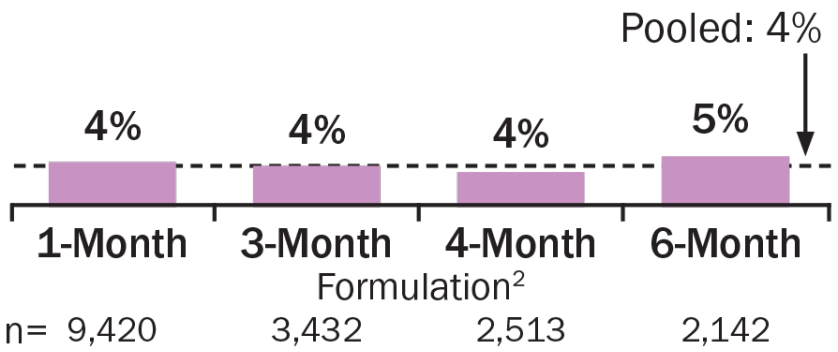
SOURCE: Adapted with permission from Crawford E.D. et al.,*The Journal of Urology*. Vol. 203, 743-750, April 2020.

27% Versus 4% of T Tests Were >50 ng/dL for Late[1] and Early/On-Time[1] Injections, Respectively

Proportion of T Tests >50 ng/dL After Early/On-Time[1] and Late[1] Injection (by Formulation)

Early/On-Time* (n=8,480)

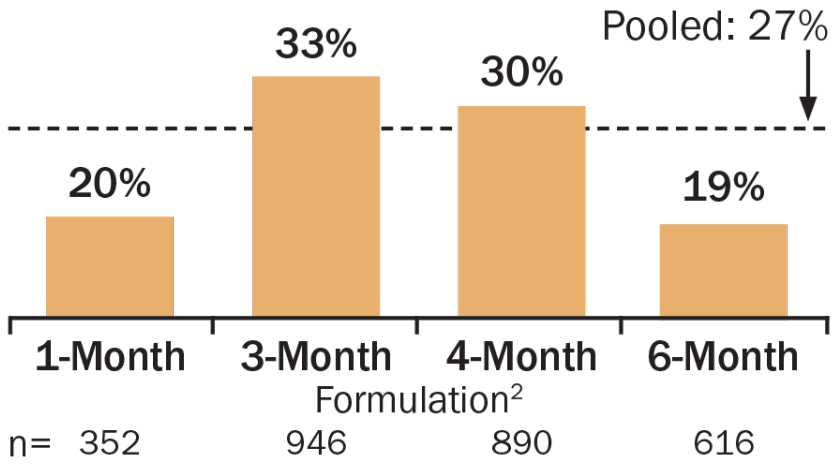
Percent of T Tests >50 ng/dL After Early/On-Time[1] Injections



* T values after early/on-time injections: mean(SD)= 21(59) ng/dL; median= 11 ng/dL; 25th percentile= 7 ng/dL; 75th percentile= 20 ng/dL

Late* (n=2,804)

Percent of T Tests >50 ng/dL After Late[1] Injections



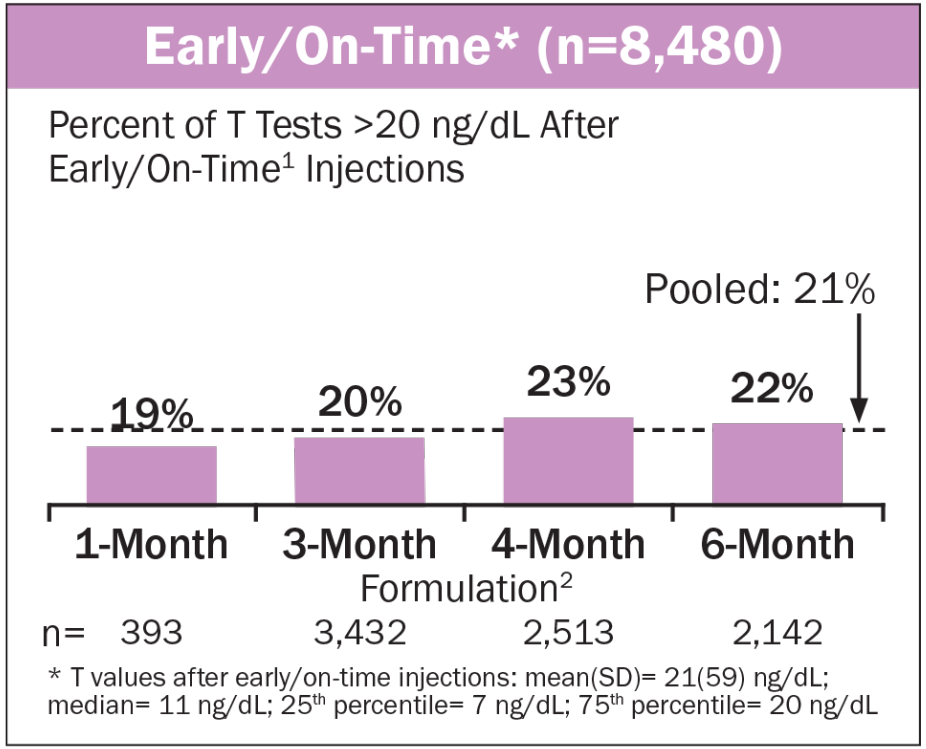
* T values after late injections: mean(SD)= 79(135) ng/dL; median= 19 ng/dL; 25th percentile=9 ng/dL; 75th percentile= 71 ng/dL

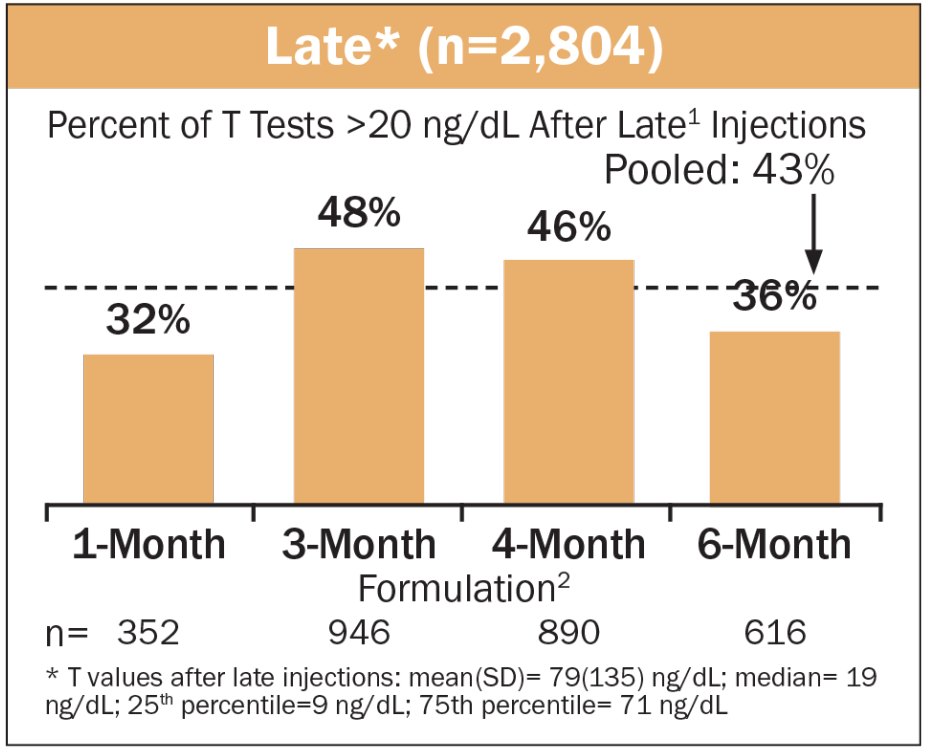
1. "Early/On-Time" if prior to, or "Late" if on/after day 33 (1-M formulation), 98 (3-M formulation), 129 (4-M formulation), or 195 (6-M formulation)
2. First admin data for 1-M formulation was excluded to remove skewed results from potential T flare seen with GnRH agonists

SOURCE: LHRH-ATTT Raw Data; Updated as of 8/19/21

43% Versus 21% of T Tests Were >20 ng/dL for Late[1] and Early/On-Time[1] Injections, Respectively

Proportion of T Tests >20 ng/dL After Early/On-Time[1] and Late[1] Injection (by Formulation)





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2. First admin data for 1-M formulation was excluded to remove skewed results from potential T flare seen with GnRH agonists

SOURCE: LHRH-ATTT Raw Data; Updated as of 8/19/21

Study Conclusions

- PSA is commonly used as a surrogate of ADT efficacy. However, as the primary goal of ADT is T reduction to castration levels, efficacy should be determined by T measurement.
- 84% of doses of LHRH agonists were administered later than scheduled (28 days or multiples thereof) in pivotal trials, and 27% of doses were late using extended month definition (32 days or multiples thereof).
- Delays in dosing substantially impacted T suppression: **43% of T tests (extended month) showed T >20 ng/dL when dosing was late and 27% showed T >50 ng/dL**.
- **Mean T was higher when dosed late (49 ng/dL and 79 ng/dL for 28-day and extended month, respectively)** vs. on-time dosing (21 ng/dL for both).
- It is highly likely that increasing adherence to ADT dosing schedules would improve T suppression in patients with PCa and potentially improve clinical outcomes, including delaying disease progression.

SOURCE: Crawford E.D. et al.,*The Journal of Urology*. 203: 743-750, April 2020.

ADT = androgen deprivation therapy; LHRH = luteinizing hormone–releasing hormone; PCa = prostate cancer; PSA = prostate-specific antigen; T = testosterone

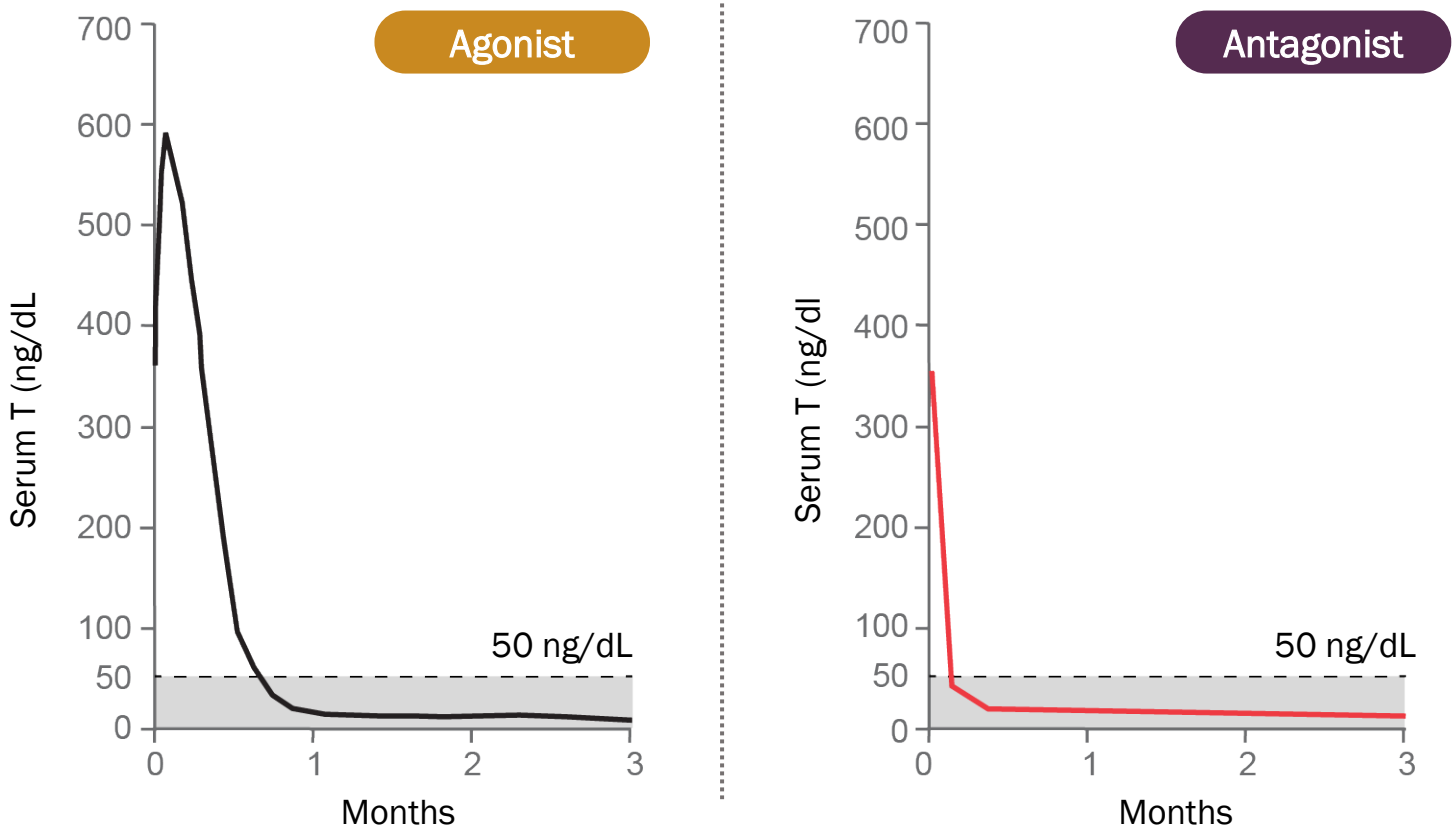
Comparative Structure of GnRH Agonists

Amino Acid Sequence

	1	2	3	4	5	6	7	8	9	10
GnRH	Glu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly-NH_2
Triptorelin	Glu	His	Trp	Ser	Tyr	D-Trp	Leu	Arg	Pro	Gly-NH_2
Goserelin	Glu	His	Trp	Ser	Tyr	D-Ser (tBu)	Leu	Arg	Pro	AzGly-NH_2
Leuprolide	Glu	His	Trp	Ser	Tyr	D-Leu	Leu	Arg	Pro	ethylamide
Histrelin	Glu	His	Trp	Ser	Tyr	D-His (tBenz)	Leu	Arg	Pro	ethylamide

Harrison GS et al. *Endocr Relat Cancer*. 2004;2:725-748.

Representative T Suppression with LHRH Therapies



T = testosterone; LHRH = luteinizing hormone-releasing hormone

History of Triptorelin

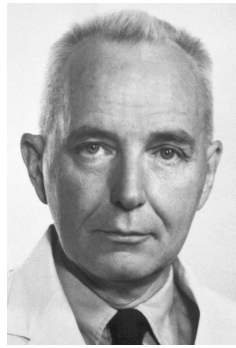
1941 — Charles Huggins and Clarence Hodges reported that marked reductions in testosterone by castration or estrogen treatment caused metastatic PCa to regress

1966 — Charles Huggins earned a Nobel Prize in Physiology or Medicine “for his discoveries concerning hormonal treatment” of PCa

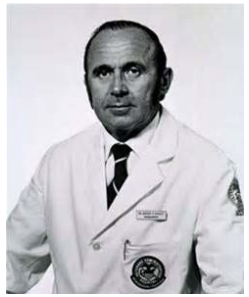
1971 — Isolation and discovery of structure of GnRH by Prof. Andrew Schally at Tulane University

1973 — First synthesis of GnRH agonist triptorelin by Prof. Andrew Schally

1977 — Andrew Schally and Roger Guillemin earned a Nobel Prize for their discoveries concerning the peptide hormone production



Charles Huggins



Andrew Schally

GnRH = gonadotropin-releasing hormone; PCa = prostate cancer

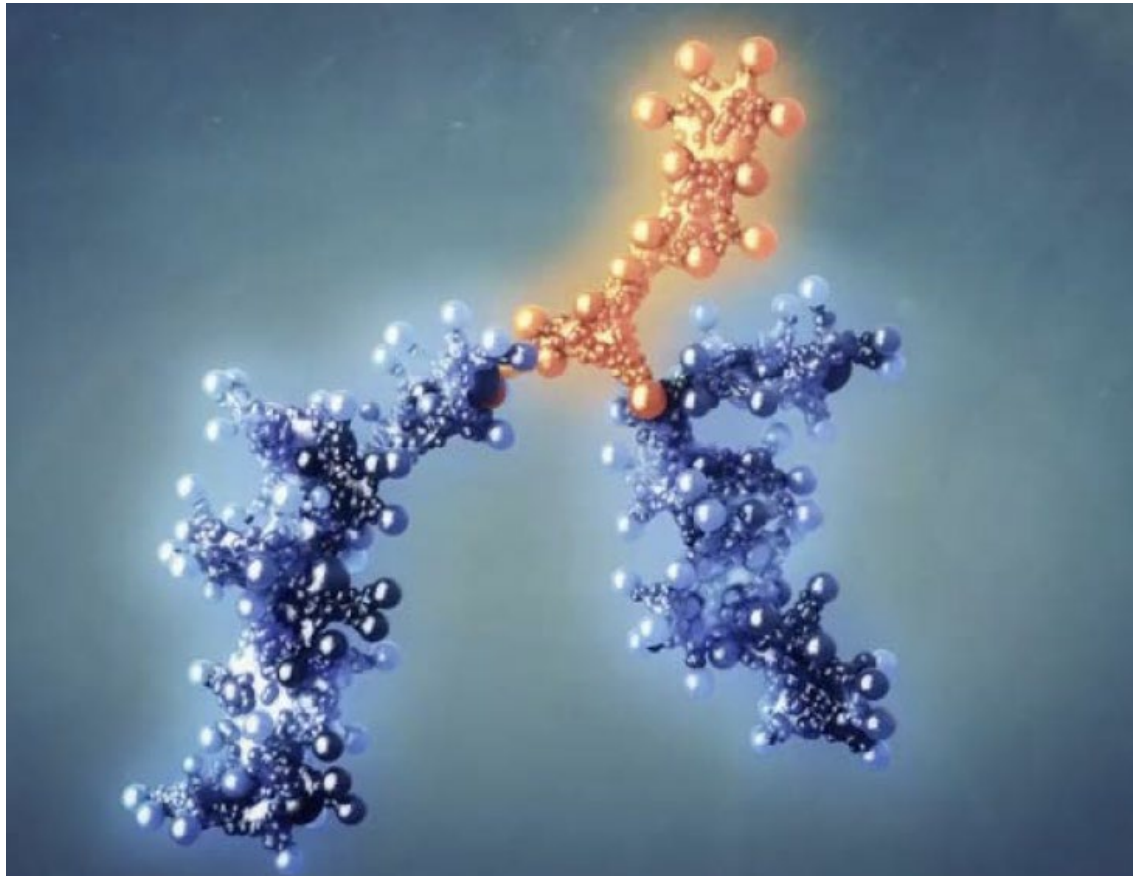
Andrew Schally's Comments. 8.15.21

"... We synthesized triptorelin and developed it for use in male and female patients at Tulane University / VA Hospital in New Orleans. Triptorelin is more potent in terms of LHRH / GnRH activity than other LHRH agonists..."

Mechanism of Action

Triptorelin differs from natural GnRH* by a single amino acid substitution at position 6[2]

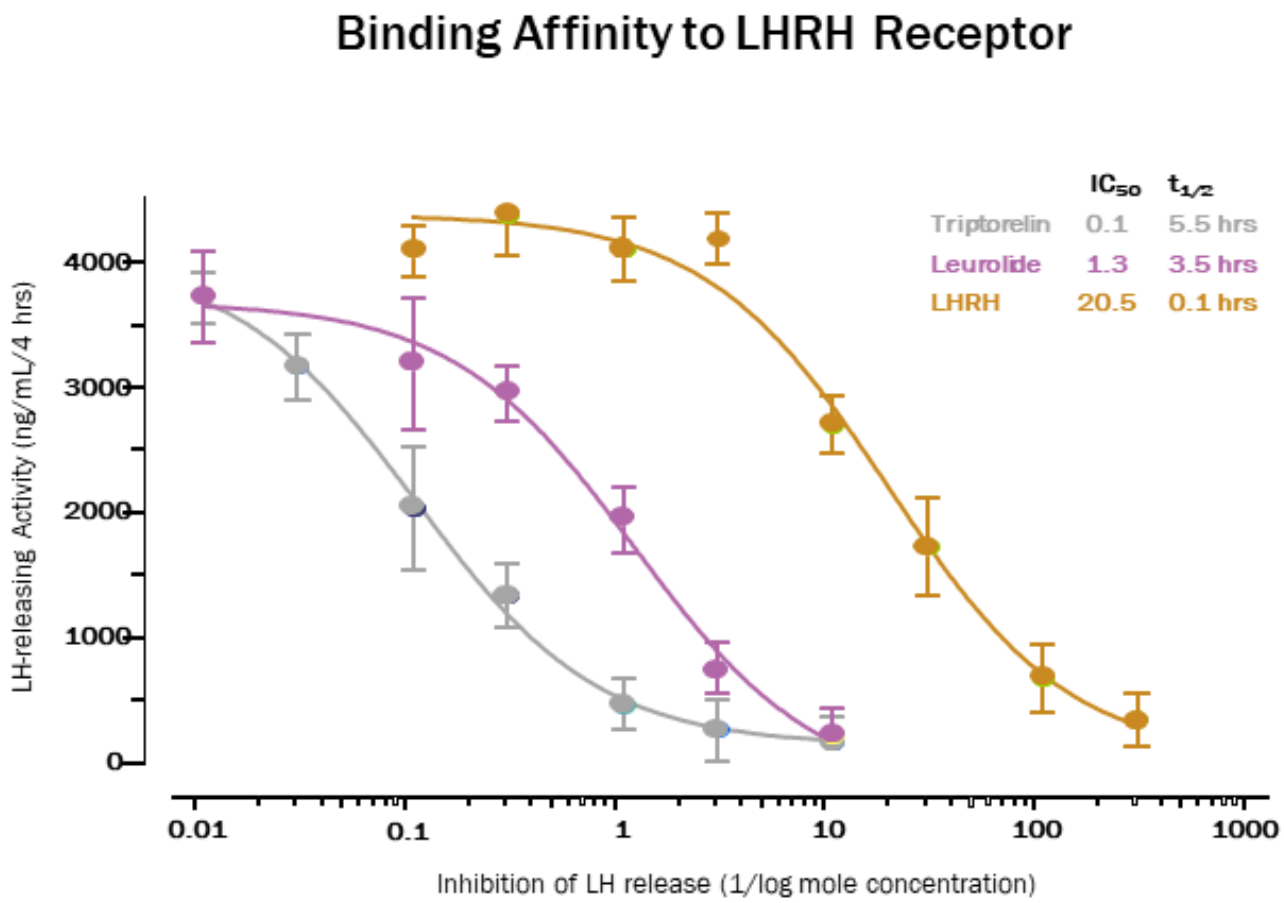
- Low potential for enzyme cleavage[1,2]
- Long half-life[1,3]
- High biologic potency[1,2]
  - 131 times more potent than native GnRH
  - 6 times more potent than an approved GnRH agonist



GnRH = gonadotropin-releasing hormone.

1. Heyns CF et al. *BJU Int* 2003;92:226–231; 2. Teillac P et al. *Horm Res* 2004;62:252–258; 3. Coy DH et al. *Biochem Biophys Res Commun* 1975;67:576–582

Triptorelin Binding Affinity



GnRH = gonadotropin-releasing hormone

1. Millar et al. XIII International Congress of Comparative Endocrinology. 1997:559-562.
2. Heyns et al. *BJU Int*. 2003;92:226-231. 3. Teillac et al. *Horm Res*. 2004;62:252-258.
4. Coy et al. *Biochem Biophys Res Comm*. 1975;67:576-582

IC_{50} = half-maximal inhibitory concentration; LH = luteinizing hormone; LHRH = luteinizing hormone–releasing hormone

Provided by Hope Elliott. Adapted from Coy DH et al. *Biochem Biophys Res Comm.* 1975;67:576-582.

Comparative Clinical Trials

Clinical Trial > BJU Int. 2003 Aug;92(3):226-31. doi: 10.1046/j.1464-410x.2003.04308.x.

Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer

C F Heyns [1], M-P Simonin, P Grosgurin, R Schall, H C Porchet, South African Triptorelin Study Group

Affiliations + expand

PMID: 12887472 DOI: 10.1046/j.1464-410x.2003.04308.x

Abstract

Objective: To compare the efficacy of monthly administrations of the luteinizing hormone-releasing hormone agonists triptorelin pamoate and leuprolide acetate to induce and maintain castrate levels of serum testosterone in men with advanced prostate cancer.

Patients and methods: Men with advanced prostate cancer were randomly assigned to receive triptorelin 3.75 mg or leuprolide 7.5 mg. The agent was injected intramuscularly every 28 days for nine injections. Primary endpoints were the percentages of men whose serum testosterone concentrations declined to and were maintained at or below castrate levels (</= 1.735 nmol/L or </= 500 ng/L) during 9 months (253 days) of treatment. Secondary endpoints were luteinizing hormone levels, bone pain, prostate specific antigen levels, quality of life, testosterone pharmacodynamics, survival, and safety variables.

Results: In all, 284 men received either triptorelin (140) or leuprolide (144). The percentage of men with castrate levels of serum testosterone was lower at 29 days for triptorelin than for leuprolide (91.2% vs 99.3%; point estimate - 8.0, 95% confidence interval - 16.9% to - 1.4%), but equivalent at 57 days (97.7% vs 97.1%). The mean (98.8% vs 97.3%) and cumulative (96.2% vs 91.2%) castration maintenance rates between 29 and 253 days were equivalent between the treatment groups. Secondary endpoints were equivalent between treatment groups except for the 9-month survival rate, which was significantly higher for triptorelin than for leuprolide (97.0% vs 90.5%; P = 0.033). Both treatments were well tolerated.

Conclusion: Triptorelin reduced testosterone concentrations less rapidly, but maintained castration as effectively as leuprolide. There was no evidence that the slower onset of castration caused deleterious effects.

Comparative Study > Investig Clin Urol. 2019 Jul;60(4):244-250. doi: 10.4111/icu.2019.60.4.244. Epub 2019 May 21.

Effectiveness of three different luteinizing hormone-releasing hormone agonists in the chemical castration of patients with prostate cancer: Goserelin versus triptorelin versus leuprolide

Myungsun Shim [1], Woo Jin Bang [1], Cheol Young Oh [1], Yong Seong Lee [1], Jin Seon Cho [1]

Affiliations + expand

PMID: 31294133 PMCID: PMC6607074 DOI: 10.4111/icu.2019.60.4.244

Abstract

Purpose: To investigate the changes in testosterone levels and rates of chemical castration following androgen-deprivation therapy (ADT) with goserelin, triptorelin, and leuprolide.

Materials and methods: We retrospectively reviewed the medical records of 125 patients with prostate cancer treated with luteinizing hormone-releasing hormone (LHRH) agonists between January 2009 and December 2015. Changes in testosterone concentration during 9 months of ADT with goserelin 11.34 mg, triptorelin 11.25 mg, and leuprolide 11.25 mg were analyzed using a mixed model. The number of patients with serum testosterone below castration levels defined as various values (<50 ng/dL, <20 ng/dL, or <10 ng/dL) at 3, 6, and 9 months were also evaluated.

Results: Of the 125 patients, 59 received goserelin, 44 received triptorelin, and 22 received leuprolide, respectively. The lowest mean testosterone levels during 9 months of treatment were achieved in patients treated with triptorelin, followed by those treated with leuprolide, and then by those treated with goserelin (p=0.001). Significant differences in chemical castration levels were observed only at <10 ng/dL, with 54.2% of goserelin, 93.2% of triptorelin, and 86.4% of leuprolide treated patients (p<0.001).

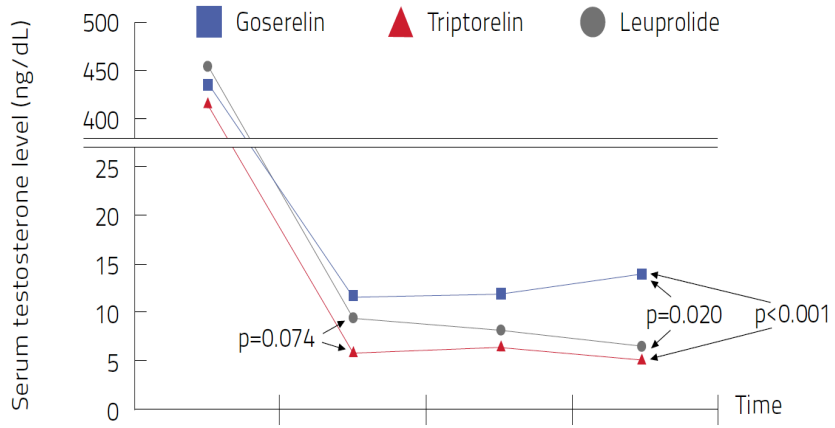
Conclusions: Three LHRH agonists showed comparable efficacy for achieving castration when the castration threshold was 50 or 20 ng/dL. However, triptorelin was the most potent LHRH agonist, achieving the lowest mean testosterone levels and the highest rate of chemical castration at <10 ng/dL testosterone.

Keywords: Antineoplastic agents; Prostate-specific antigen; Prostatic neoplasms; Testosterone.

Triptorelin Was the Most Potent GnRH in Terms of Achievement of Testosterone Levels <10 ng/dL

Lowest mean serum testosterone levels in patients treated with triptorelin vs. leuprolide and goserelin[1]*

Mean serum testosterone level after ADT according to different GnRH agonists (patients with GnRH monotherapy)

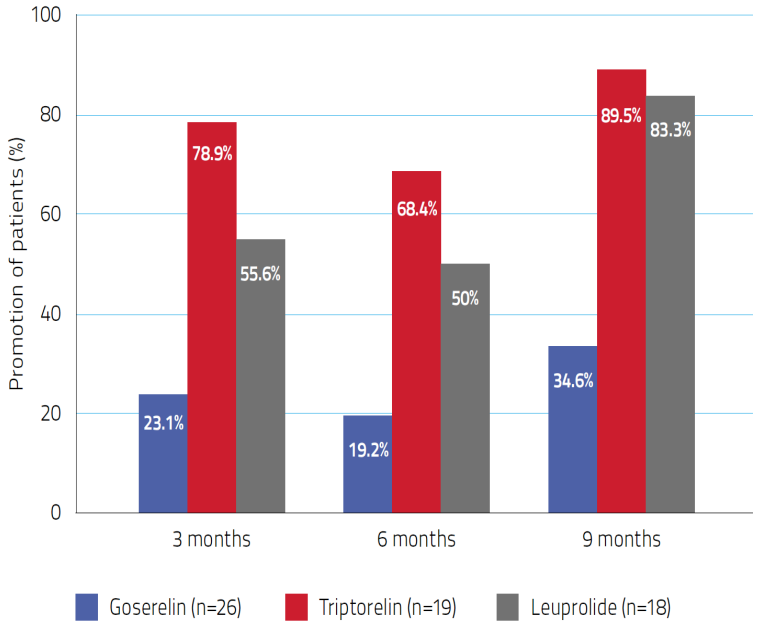


Mean+SD	Baseline	3 months	6 months	9 months
Goserelin	441.3 ± 121.4	11.5 ± 8.4	12.1 ± 6.2	14.1 ± 15.4
Triptorelin	422.8 ± 118.2	6.1 ± 5.1	6.5 ± 4.6	5.1 ± 3.1
Leuprolide	460.2 ± 139.7	9.6 ± 8.2	8.7 ± 6.7	6.8 ± 6.0

Significantly lower mean testosterone level in patients treated with triptorelin vs. goserelin ($p < 0.001$)[1]

89.5% of patients treated with triptorelin achieved testosterone levels <10ng/dL[1]

Proportion of patients with castration levels <10 ng/dL at 3, 6 and 9 months after treatment with GnRH agonist monotherapy



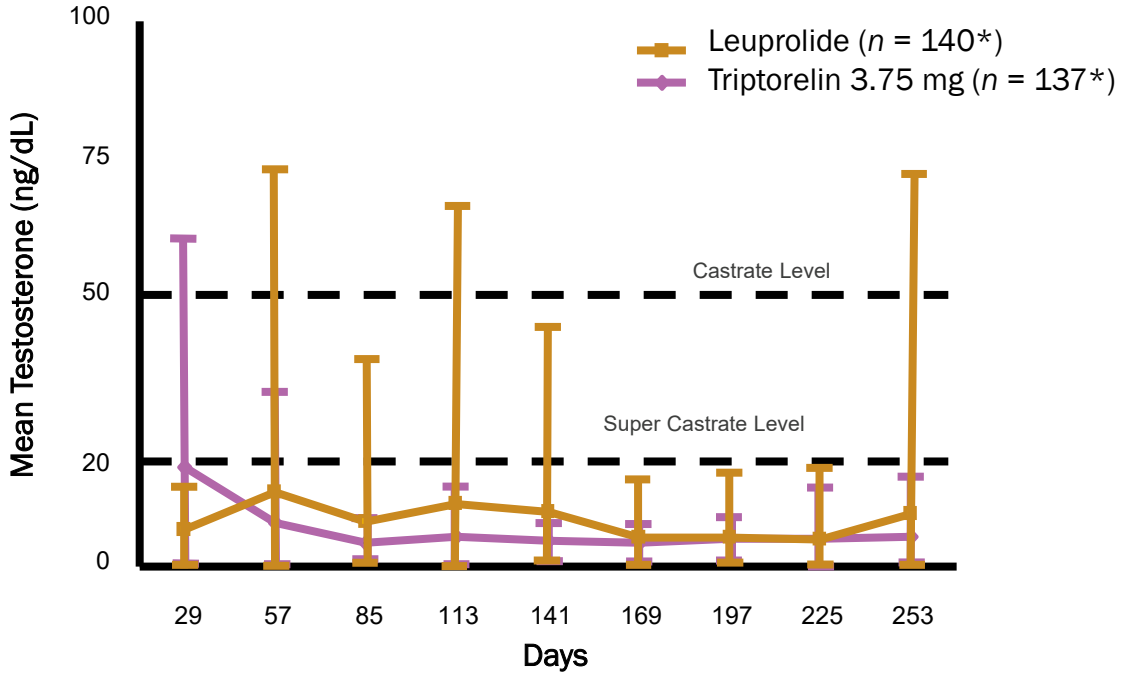
- Castration <10 ng/dL observed in 89.5% of triptorelin- and 83.3% of leuprolide-treated patients at 9 months[1]
- Castration <10 ng/dL significantly lower (34.6%) with goserelin at 9 months ($p < 0,001$)[1]
- Castration <10 ng/dL in all patients (ADT and bicalutamide):
  - 93.2% of triptorelin-treated patients ($n = 44$) vs. 86.4% of leuprolide- ($n = 22$) and
  - 54.2% of goserelin-treated patients ($n = 59$) ($p < 0,001$)[1]

ADT = androgen deprivation therapy; GnRH = gonadotropin hormone–releasing hormone. 1. Shim M, et al. *Investig Clin Urol* 2019;60:244–250

* Retrospective study of 125 medical records of patients with locally advanced or metastatic prostate cancer treated with LHRH agonists between January 2009 and December 2015 in one South Korean center. It aimed to evaluate the effectiveness (changes in testosterone levels and rates of chemical castration following ADT) of triptorelin (11.25 mg), leuprolide (11.25 mg), and goserelin (11.34 mg).

Testosterone Suppression: Triptorelin (1 month) vs. Leuprolide (1 month)

- 4 triptorelin patients escaped castration at least once during the study[1,2]
- 11 leuprolide patients escaped castration at least once during the study[1,2]



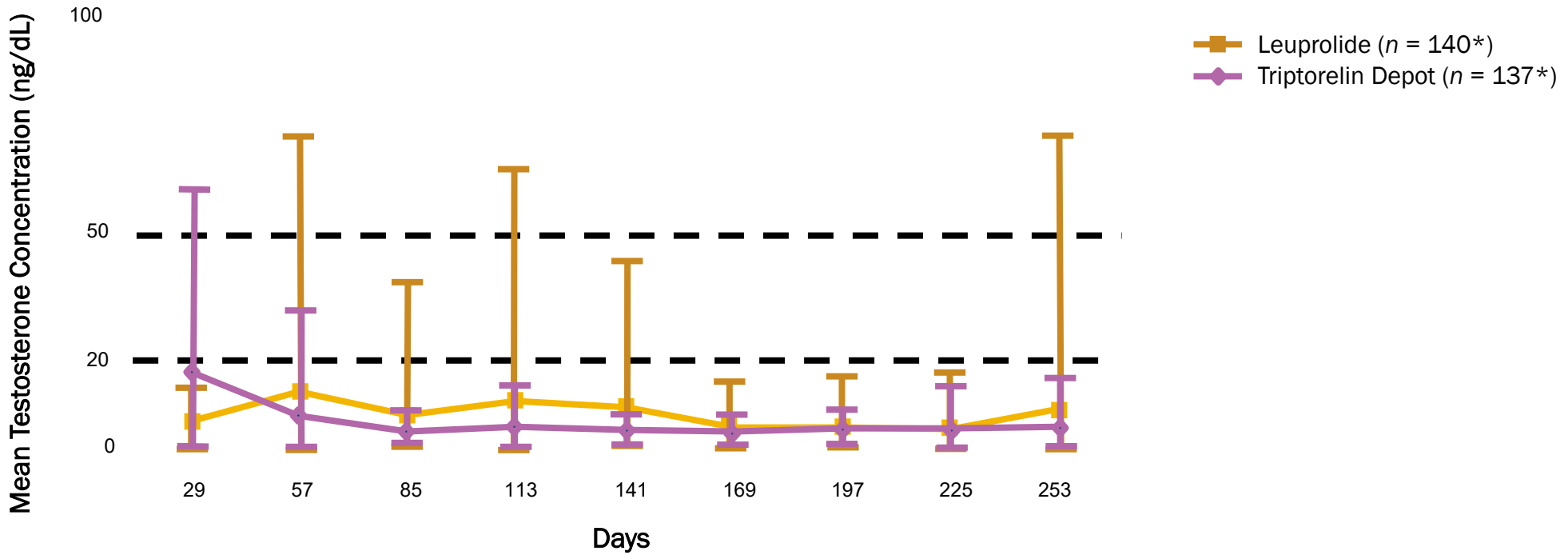
	Triptorelin 3.75 mg	Leuprolide 7.5 mg
Achievement of Castration Day 29 (% of patients)	91.2 (125/137)	99.3 (139/140)
Cumulative Maintenance of Castration Months 2 through 9 (% of patients)	96.2	91.2

*Intent to treat. At day 253, *n* = 121 for leuprolide and 119 for triptorelin 3.75 mg.

1. Data on file, Verity Pharmaceuticals. DEB-96-TRI-01 (second phase), June 1999. 2. Heyns CF et al. *BJU Int*. 2003;92:226-231.

Mean Serum Testosterone Concentration

Mean (± SD) Serum Testosterone Concentrations on Days 29–253 in Patients Treated with Triptorelin Depot or Leuprolide (Intent to Treat)

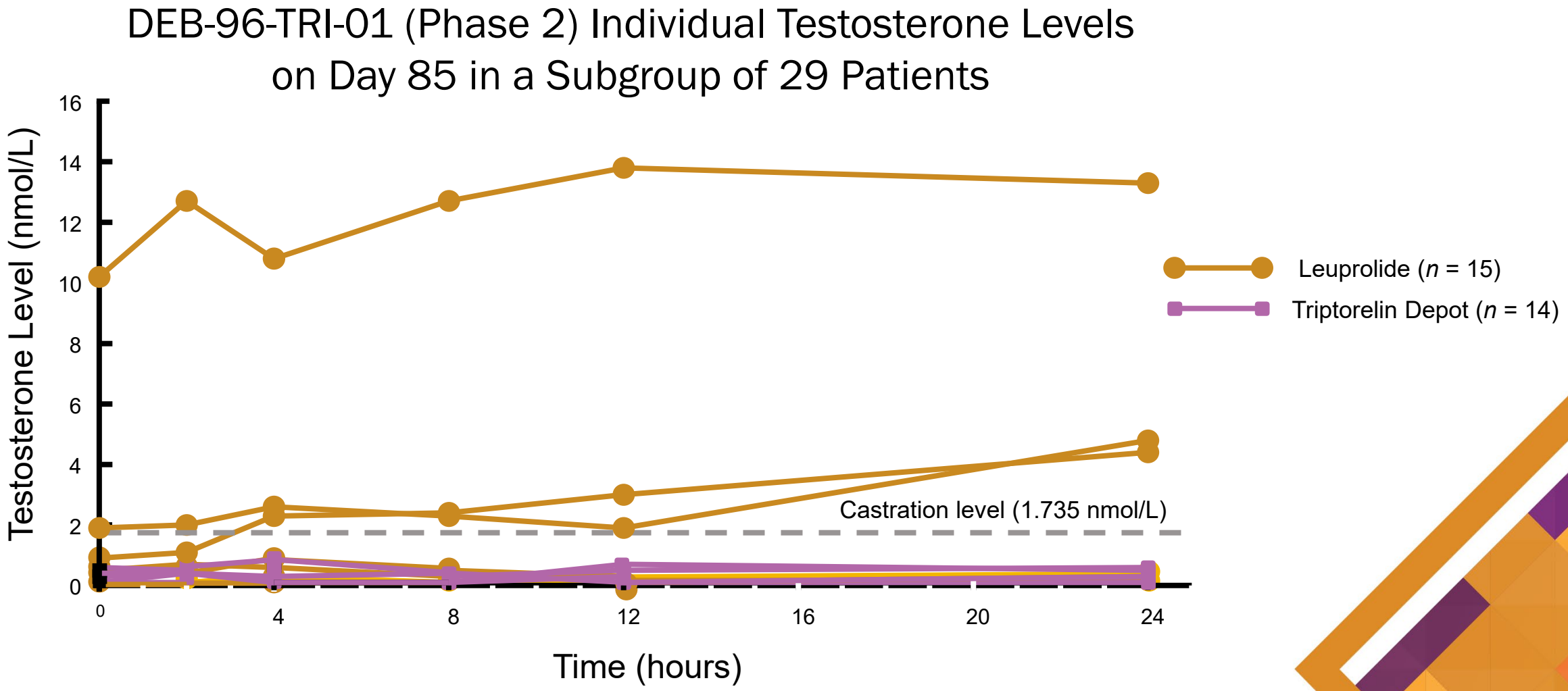


*At day 253, *n* = 121 for leuprolide and 119 for triptorelin Depot.

Patients Escaping Castration

	Triptorelin (*n* = 140)	Leuprolide (*n* = 144)
No. patients escaping, months 2–9 n (# of occurrences)	4 (5)	11 (18)

Subgroup Analysis of Castration Maintenance



Secondary End Points

- Bone pain and analgesic use were not different between treatment groups
- Reductions in PSA levels by day 253 were 97.1% and 97% for triptorelin pamoate depot and leuprolide acetate, respectively
- Baseline and end point medians for all quality-of-life parameters were comparable between groups
- Survival at 9 months: 97.0% for triptorelin pamoate depot vs. 90.5% for leuprolide acetate ($P = 0.033$)

Heyns et al, *BJU International* 92,226-231

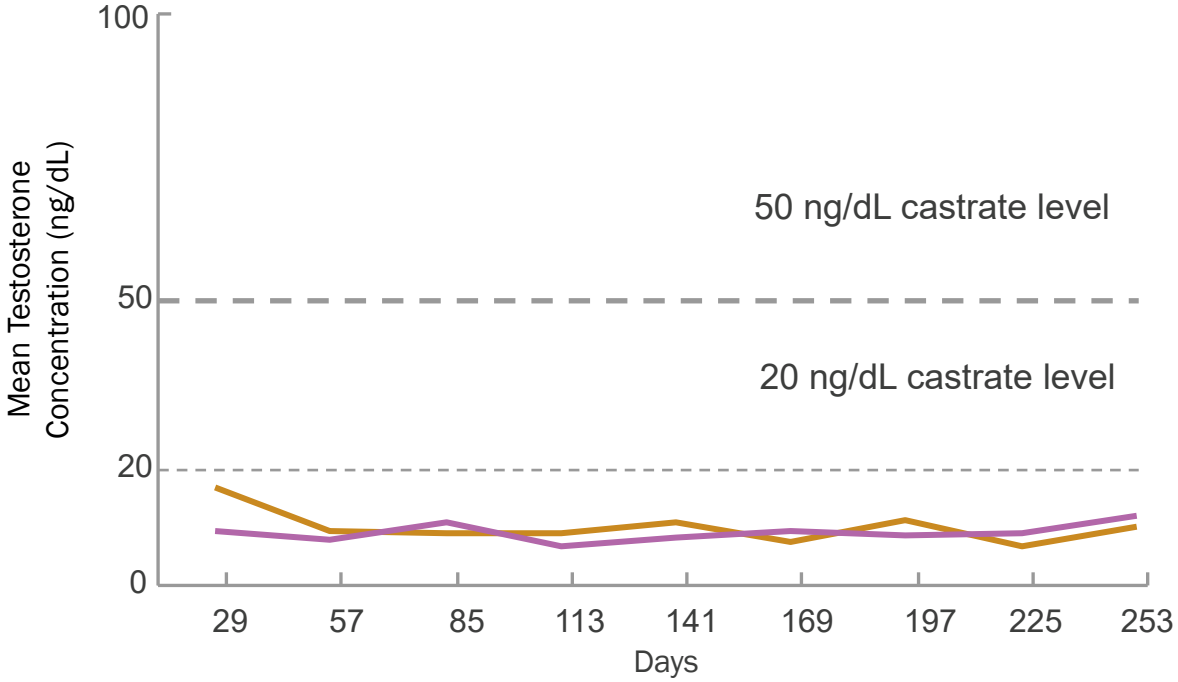
Triptorelin 3.75 and 11.25 mg

- Two-phase clinical trial[1,2]
  - Main inclusion criteria: Prostate cancer staged $T_{3\text{-}4}N_XM_X$ or $T_XN_1M_X$ or $T_XN_XM_1$ or rising PSA after failed local therapy
- Serum testosterone level >144 ng/dL
  - Life expectancy >18 months
- **Phase 1:** To determine whether triptorelin 11.25 mg is as effective as triptorelin 3.75 mg[1]
  - Primary objectives: Achieve castrate levels of testosterone at day 29 and maintain these levels without escape from month 2 through month 9
- **Phase 2:** To determine whether triptorelin 3.75 mg is as effective as the active comparator (**Leuprolide** 7.5 mg QM)[2]
  - Primary objectives: Achieve castrate levels of testosterone at day 29 and maintain these levels through months 2 to 9

1.Data on file, Verity Pharmaceuticals, DEB-96-TRI-01 (first phase), July 1999.
2.Data on file, Verity Pharmaceuticals, DEB-96-TRI-01 (second phase), June 1999.

Phase 1: Mean Serum Testosterone Concentrations Over Time (1- and 3-Month)

- Mean testosterone levels were ≤8.1 ng/dL in patients treated with triptorelin 3.75 mg[1]
- Mean testosterone levels were ≤12.4 ng/dL in patients treated with triptorelin 11.25 mg[2]



The clinical benefits of maintaining testosterone levels <20 ng/dL vs. <50 ng/dL have not been prospectively studied.

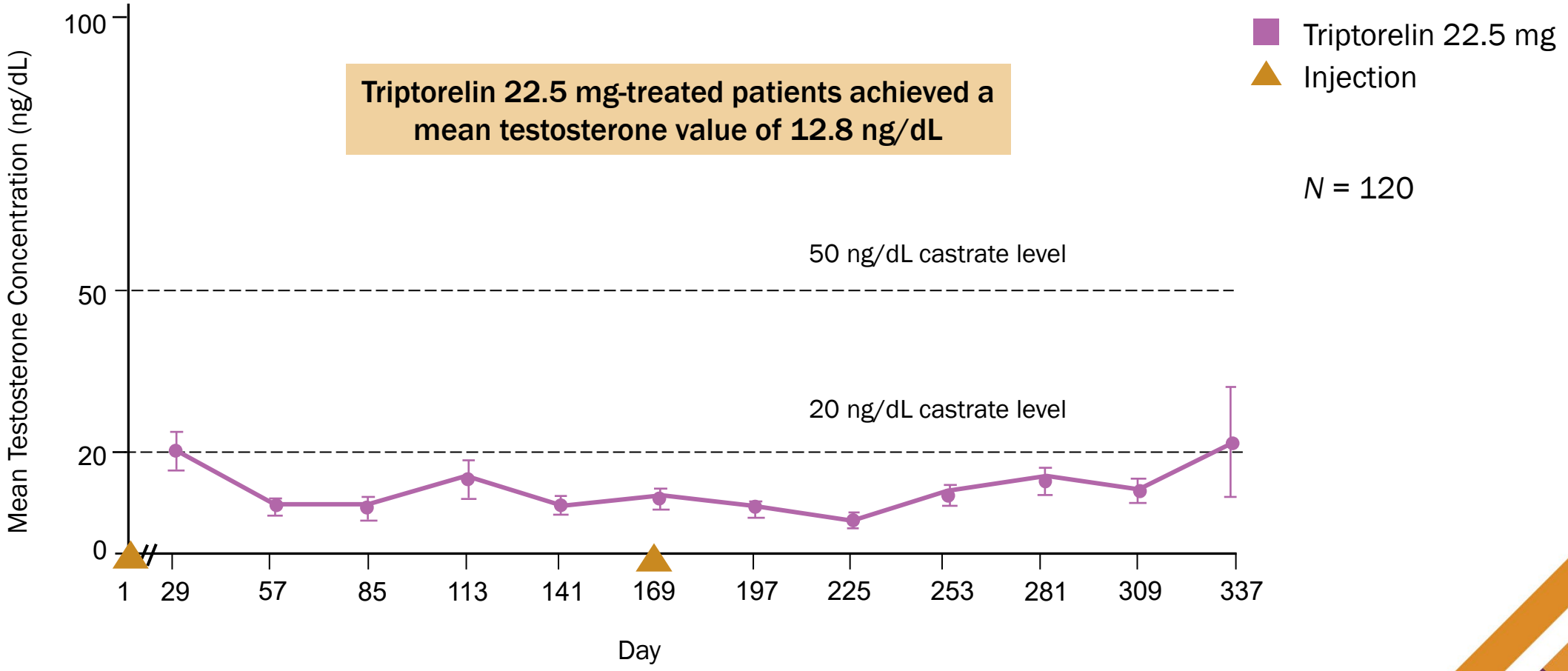
1.Data on file, Verity Pharmaceuticals. DEB-96-TRI-01 (second phase), June 1999.
2.Data on file, Verity Pharmaceuticals. DEB-96-TRI-01 (first phase), July 1999.

Testosterone Concentrations: Mean ± SD Serum Testosterone (ng/dL)

	Scr	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253
Triptorelin Pamoate LA 11.25 mg											
Mean	324.86	334.39	8.09	5.20	9.83	4.62	6.07	7.80	6.07	7.80	12.43
SD	132.95	150.00	25.43	14.45	34.39	5.49	8.38	24.86	7.23	14.16	42.77
Triptorelin Pamoate Depot 3.75 mg											
Mean	355.78	347.69	15.61	6.94	6.94	7.80	10.40	5.49	10.12	5.78	10.98
SD	135.84	153.76	40.75	15.90	19.08	26.30	43.06	6.36	57.51	7.51	58.96

Data on file, Verity Pharmaceuticals.

Testosterone Suppression at 22.5 mg



Data on file, Verity Pharmaceuticals, DEB-TRI6M-301 Clinical Study Report, May 2008.

Efficacy of Triptorelin 1, 3, and 6 Months

	Triptorelin 1-Mo n=164 9 injections over 9 months[1]	Triptorelin 3-Mo n=171 3 injections over 9 months[1]	Triptorelin 6-Mo n=120 2 injections over 9 months[2]	Triptorelin 6-Mo n=120 2 injections over 12 months[2]
Achievement rate on Day 29 (% of patients) (95% CI)	92.7% (87.6; 96.2)	97.7% (94.1; 99.4)	97.5% (92.9; 99.5)	97.5% (92.9; 99.5)
Maintenance Rate (Day 57 to end)	94.2%[3] (90.6; 97.9)	94.4%[3] (90.9; 97.9)	94.1%[3] (89.9; 98.4)	93.3% (92.9; 99.5)
Patients below castration at end of trial	99.2%	96.6%	-	98.3%

This table summarizes the main efficacy and maintenance data on the triptorelin pamoate 1-, 3- and 6-month formulations studied over 9 or 12 months in terms of achievement of castration at 1 month and maintenance of castration from month 2 to end of the study.

Data on file, Verity Pharmaceuticals, DEB-96-TRI-01 (first phase), July 1999

Adverse Events

	Triptorelin 3.75 mg (n = 140)	Active Comparator (n = 144)	Triptorelin 22.5 mg (n = 120)
Any adverse event, %	93.6	95.1	95.8
Related adverse event*, %	74.3	69.4	N/A
Intensity, %			
Mild	83.6	84.7	86.7
Moderate	60.7	70.1	47.5
Severe	24.3	34.7	14.1
Most frequent, %			
Hot flushes	58.6	54.2	71.7
Skeletal pain	21.4	16.7	10.0
Headache	13.6	18.8	7.5
Constipation	15.0	15.3	

Heyns CF et al. *BJU Int.* 2003;92:226-231; **Crawford ED, et al. *Prostate Cancer Prostatic Dis* 2019;22:24–38**

Active comparator = leuprolide 7.5 mg..

Key Take-Home Messages

- ADT is foundational therapy for advanced prostate cancer
- ADT considerations
  - orchiectomy, antiandrogens, LHRH therapy
  - speed of onset, flare
  - **achieve and maintain T <20**
  - **low nadir level, minimize escapes/microsurges**
  - intermittent therapy?
  - safety profile
  - patient factors
  - cost
- Monitoring is critical
  - PSA and T, BMD, compliance
- Management of CVD patient
  - glucose, lipids, BP, weight
  - exercise, smoking, diet, alcohol
  - selection of ADT
  - co-care with cardiologist
- Onset of CRPC, API initiation
  - continue effective ADT
  - **select appropriate drug**
  - identify and manage AEs
  - monitor for drug resistance

ADT = androgen deprivation therapy; AE = adverse effect; BMD = bone mineral density; BP = blood pressure; CVD = cardiovascular disease; LHRH = luteinizing hormone–releasing hormone; PSA = prostate-specific antigen; T = testosterone

Monitoring During ADT

- Confirm efficacy
  - routinely measure PSA and T
- Monitor for Adverse Events
  - CVD (e.g., lipids, BP, weight, smoking)
  - glucose
  - BM density
- Therapy compliance
  - injection timing
- Caregiver feedback
- Shared care

Review and modify therapies if necessary

BP = blood pressure; CVD = cardiovascular; PSA = prostate-specific antigen; T = testosterone