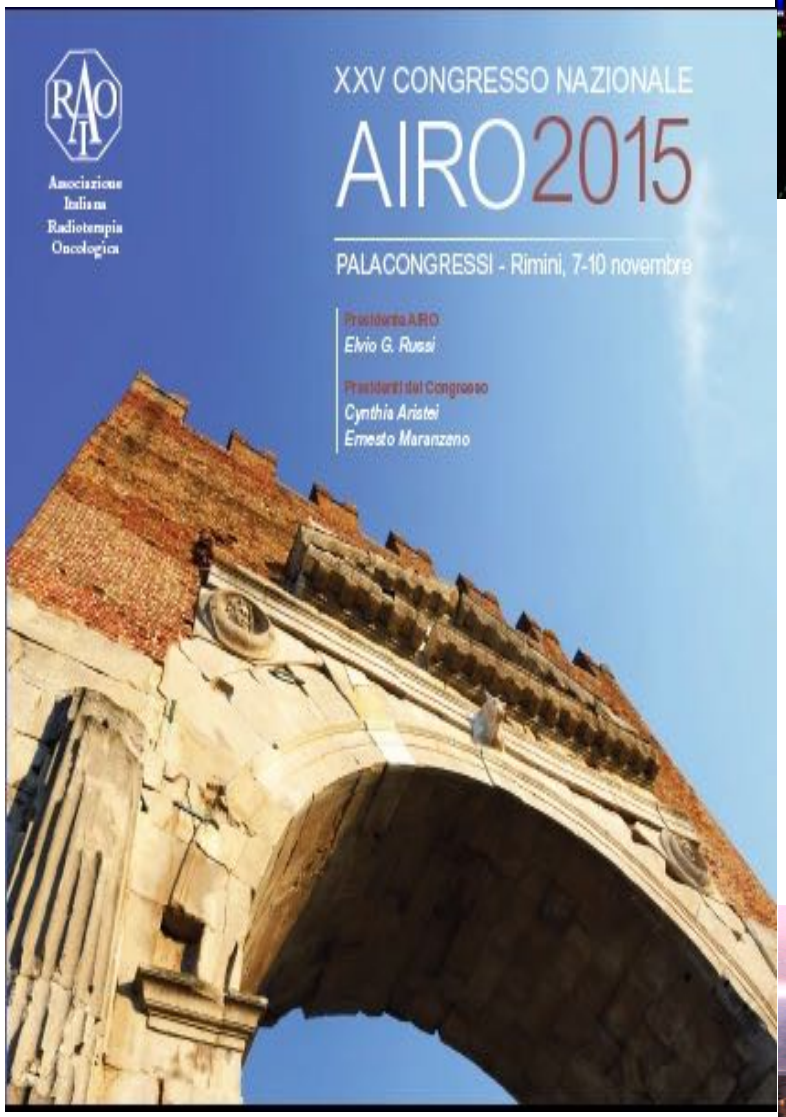

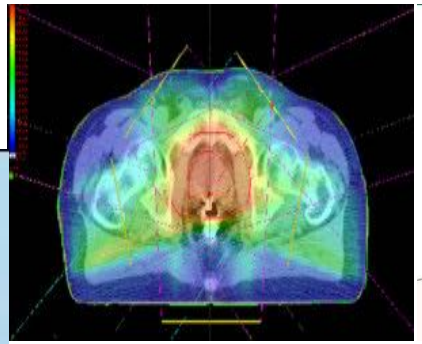

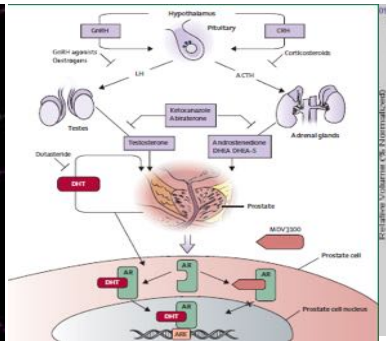

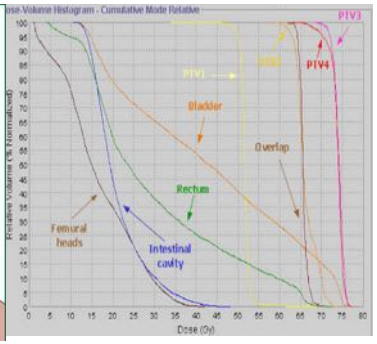

ADT efficacy and safety: are all GnRH analogues the same?

Vittorio Vavassori
U.O. Radioterapia, Humanitas Gavazzeni Bergamo

Storia naturale del ca prostatico

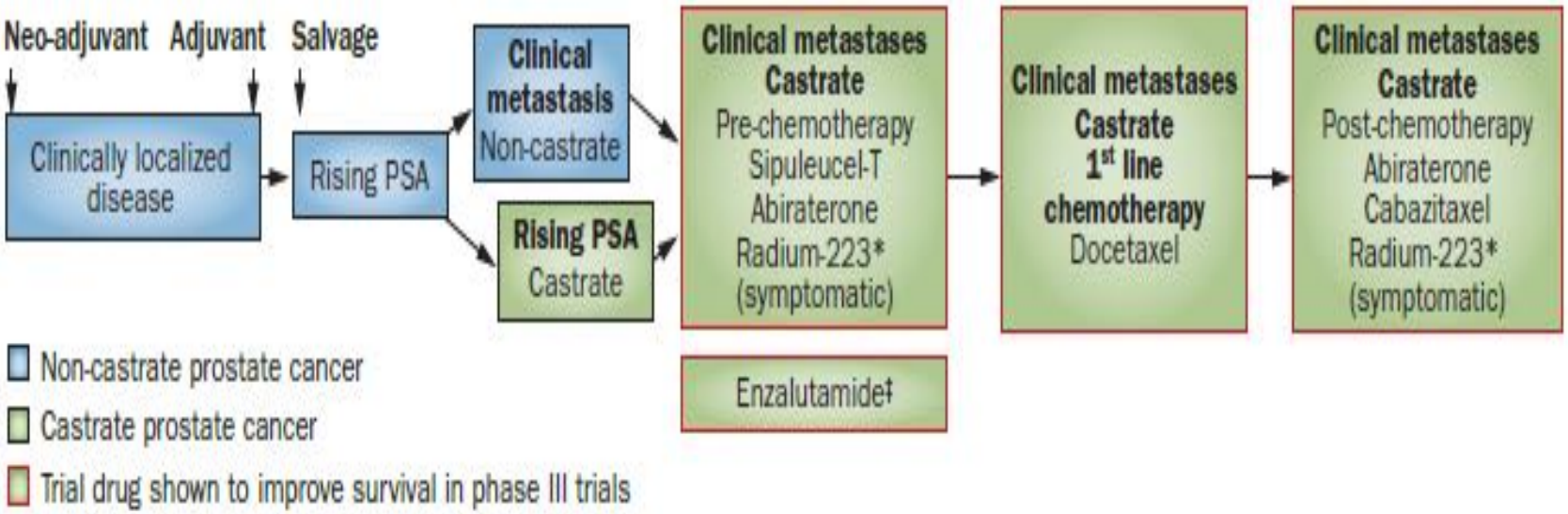

Figure 1 | Clinical states of prostate cancer. Adapted with permission from Scher & Heller, *Urology* **55**, 323–327 (2000).[1] *Approved by the FDA to treat cancer that has spread to bones but not to other organs. ‡Shown to improve survival in a phase III trial, and under Priority Review by the FDA. Abbreviation: PSA, prostate-specific antigen.

Vantaggi / svantaggi delle classi di ADT

Treatment	Advantages	Disadvantages
Orchidectomy	• Still considered the gold standard for ADT • Fast and pronounced testosterone control • Simple surgical procedure • Can be performed using local anaesthetic • No problems with compliance	• Negative psychological effect • Irreversible • Broad spectrum of side effects (vasomotor, sexual, metabolic, physical, cognitive, bone loss) • Surgical complications possible
Oestrogens	• Effective testosterone suppression • Overall survival comparable with orchidectomy • Oral or parenteral application	• Increased risk of cardiovascular effects and mortality with oral use (particularly with diethylstilboestrol 5 mg) • Not recommended by European Association of Urology as first-line treatment
Anti-androgens	• Non-steroidal anti-androgen monotherapy can be used in locally advanced prostate cancer as an alternative to castration • May preserve libido, physical performance and bone mineral density (leading to improved quality of life/compliance) • Used with other ADTs for complete androgen blockade (reduces risk of LHRH agonist 'flare') • Reversible • Oral application	• Overall survival with non-steroidal anti-androgens may be lower than with orchidectomy • May be less effective in high tumour burden (metastatic disease) • Steroidal anti-androgens associated with hepatotoxicity, cardiovascular toxicity, loss of libido, impotence • Non-steroidal anti-androgens associated with hepatotoxicity, gynaecomastia, breast pain, hot flushes

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F. Schröder*, E.D. Crawford†, K. Axcrona‡, H. Payne§ and T.E. Keane¶

Vantaggi / svantaggi delle classi di ADT

LHRH agonists	• Overall survival appears to be similar as for orchidectomy • Standard of care for advanced prostate cancer/high-risk localized disease (+ radiotherapy): associated with improved survival in combination with radiotherapy • Reversible	• Side effects comparable with surgical castration • Initial testosterone surge delays therapeutic benefit and may lead to clinical symptoms (clinical flare) • Potential tumour-promoting effects of increased testosterone
GnRH antagonists	• Reversible • Direct and logical mechanism of action • Fast, profound and sustained testosterone and PSA suppression • Prolong PSA progression-free survival[a] • Efficacy and safety maintained in long-term (>3 years)[a] • No initial testosterone surge or subsequent microsurges • Beneficial effects on bone markers (serum alkaline phosphatase)[a]	• Hormonal side-effect profile comparable with LHRH agonists • Higher incidence of injection-site reactions than leuprolide[a] • No 3-month formulation • The antagonist abarelix has been associated with the risk of systemic allergic reactions; no systemic anaphylactic reactions were observed during the clinical development of degarelix in patients with prostate cancer

[a] *Reported for degarelix only.*

BJUI SUPPLEMENTS

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F. Schröder*, E.D. Crawford†, K. Axcrona‡, H. Payne§ and T.E. Keane¶

ADT: quando?

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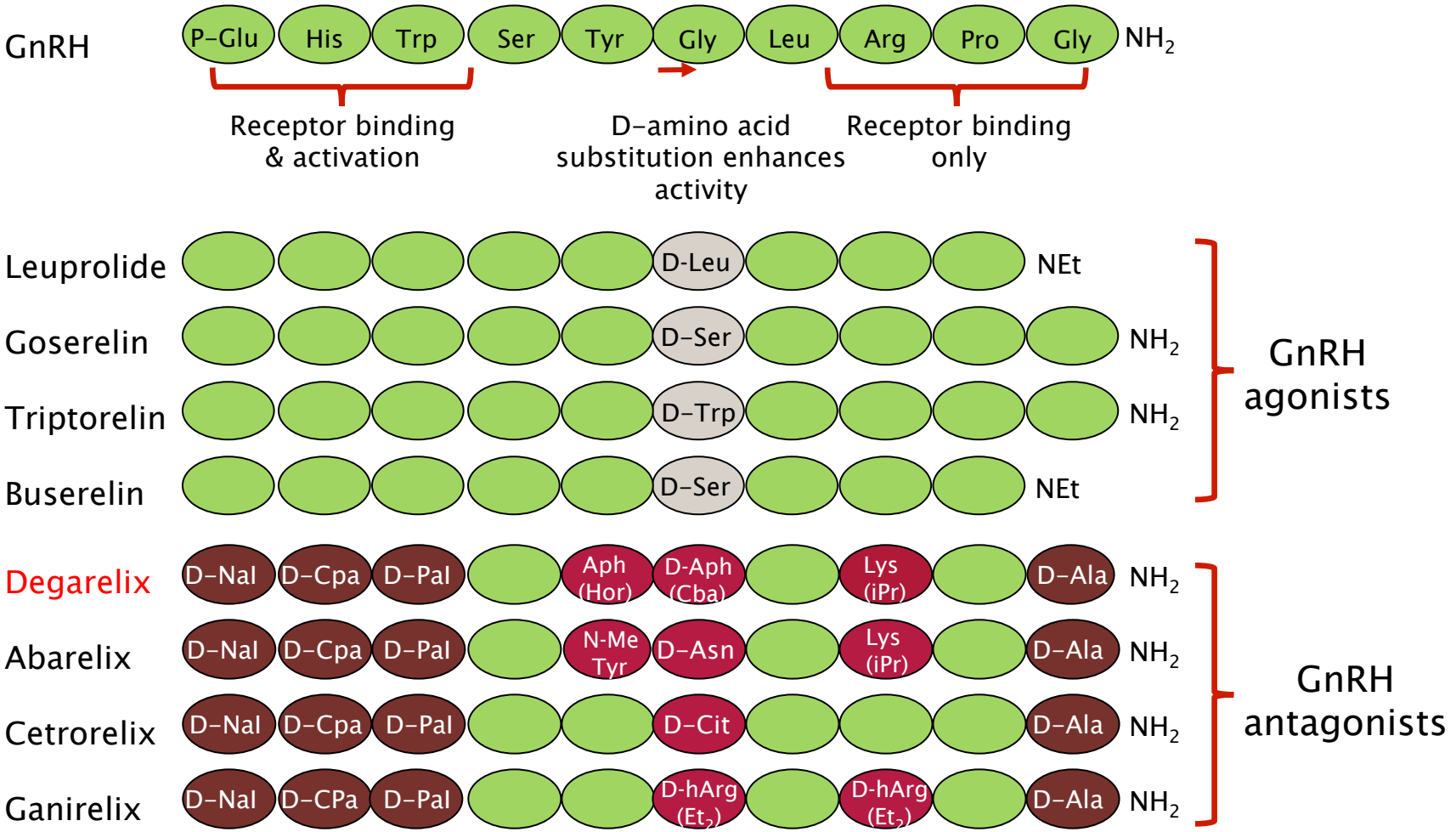
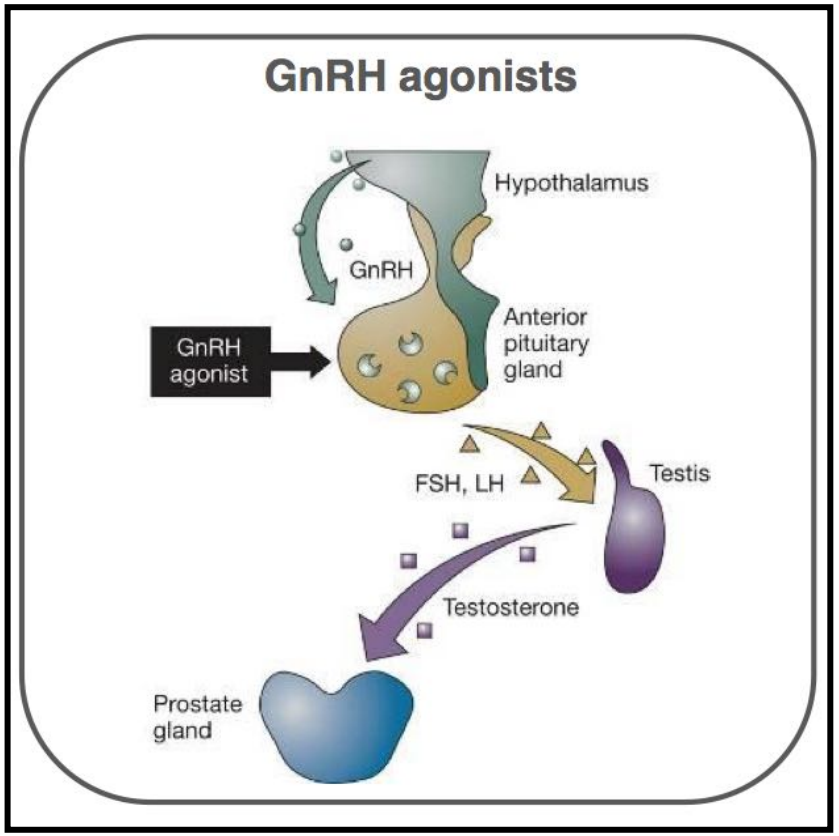
- ADT is recommended for pts unfit for radical local treatment.
- Neoadjuvant / concurrent ADT is recommended for four to six months in patients receiving radical radiotherapy for high-risk disease and should be considered in patients with intermediate-risk disease. Adjuvant hormonal therapy for two to three years is recommended for men who are at high risk of prostate cancer mortality.
- ADT is recommended for locally advanced and metastatic prostate cancer.
- GnRH analogues are the drugs of choice in locally advanced and metastatic prostate cancer (anti-androgen monotherapy is not recommended). Anti-androgens are indicated to overcome the initial surge in testosterone that occurs when LHRH agonists are started and also after PSA progression while pt is taking LHRH – agonist/antagonist
- High dose bicalutamide is indicated for localized prostate cancer and in biochemical relapse.

Strutture chimiche: Analoghi del GnRH



Meccanismo d'azione dei GnRH-agonisti

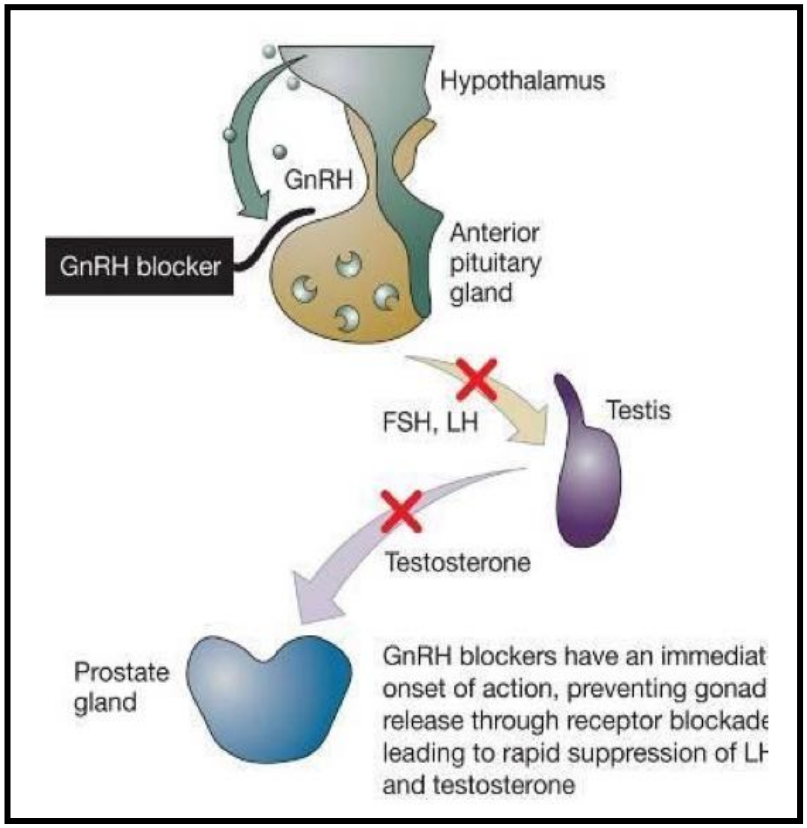
GnRH agonisti



- Effetti acuti
  - ➔ Picco immediato di FSH, LH e testosterone
- Effetti cronici
  - ➔ Ritardata soppressione di testosterone e LH, surge (clinical flare) e microsurges a iniezioni ripetute
  - ➔ Soppressione iniziale ma non mantenuta di FSH

Meccanismo d'azione dei GnRH-antagonisti

GnRH antagonisti



- Effetti acuti
  - ➔ Immediata soppressione di FSH, LH e testosterone
- Effetti cronici
  - ➔ Soppressione prolungata di FSH, LH e testosterone
  - ➔ No surge (clinical flare), no microsurges a iniezioni ripetute

Non-steroidal antiandrogen monotherapy compared with luteinizing hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer: a Cochrane systematic review

Frank Kunath*†‡, Henrik R. Grobe†§, Gerta Rücker¶, Edith Motschall¶, Gerd Antes†, Philipp Dahm**††, Bernd Wullich*‡ and Joerg J. Meerpohl†

BJUI
BJU International

BJU Int 2015; 116: 30-36
wileyonlinelibrary.com

11 studies – 3060 pts
Locally advanced, N+, M+
Different type of non steroidal AA and dose
4 studies non MTS, 4 studies MTS, 3 mixed

OS , clinical progression rate, treatment failure and discontinuation as a result of adverse event were significantly decreased w non-steroidal AA

Non steroidal AA not associated w increased Cancer Specific Mortality

Non-steroidal antiandrogen monotherapy compared with luteinizing hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer: a Cochrane systematic review

Frank Kunath*†‡, Henrik R. Grobe†§, Gerta Rücker¶, Edith Motschall¶, Gerd Antes†, Philipp Dahm**††, Bernd Wullich*‡ and Joerg J. Meerpohl†

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BJU Int 2015; 116: 30–36
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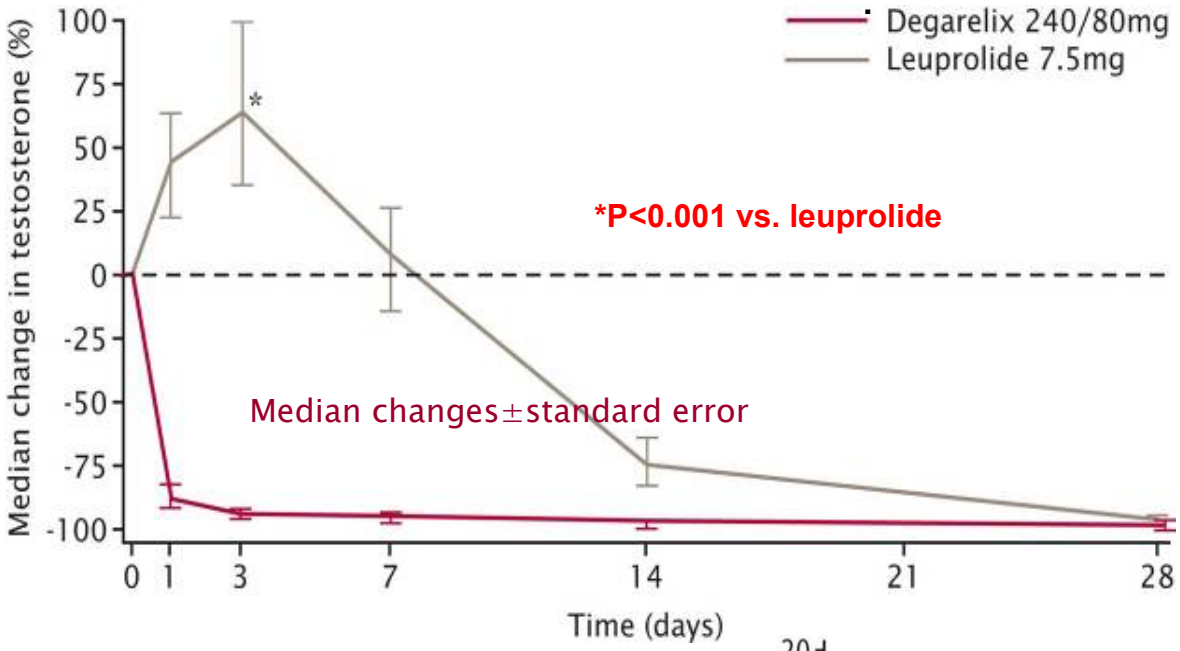
Subgroup: disease stage
No significant difference in OS in non-MTS pts
Significant difference in OS in MTS pts

Subgroup (post hoc analisys): non-MTS pts and dose of AA
No difference btw different doses(150, 450, 600 mg bicalutamide)

Subgroup (post hoc analysis): MTS pts and dose of AA
Reduceed OS w 50, 150 mg bicalutamide
No significant difference w high dose bicalutamide

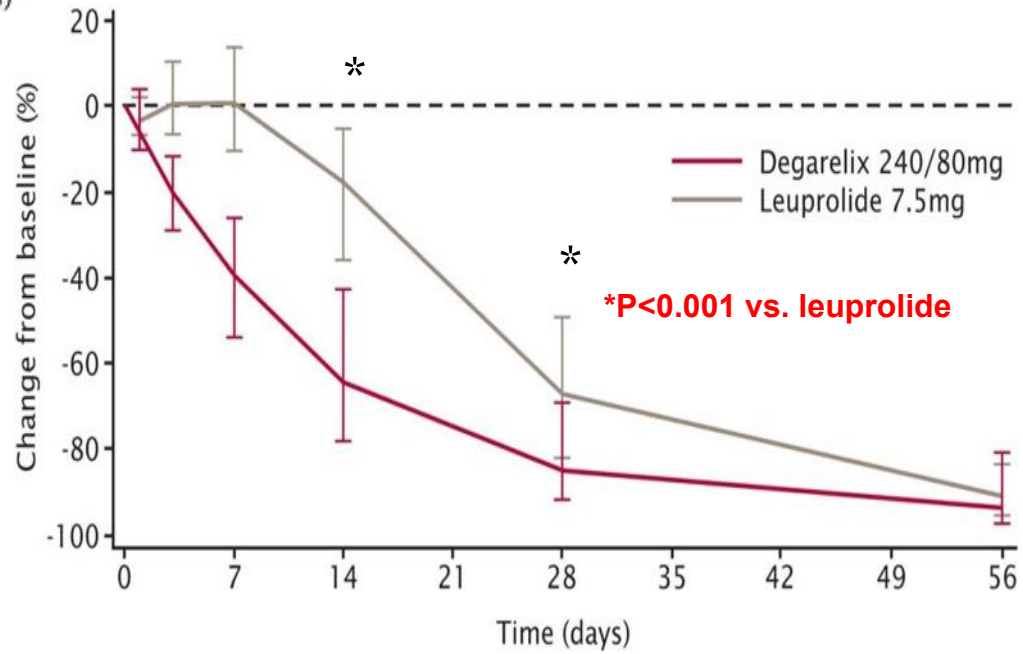
AA: higher risk of breast pain, gynecomastia; lower risk of hot flushes

Direct comparative studies btw (ant)agonists



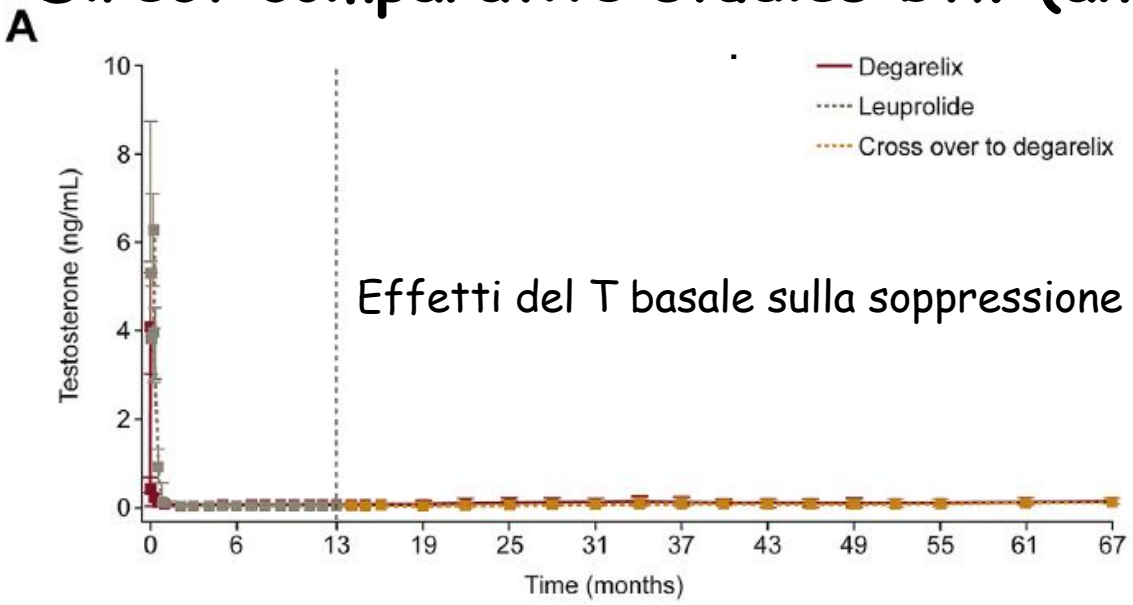
Azione sul testosterone

Azione sul PSA



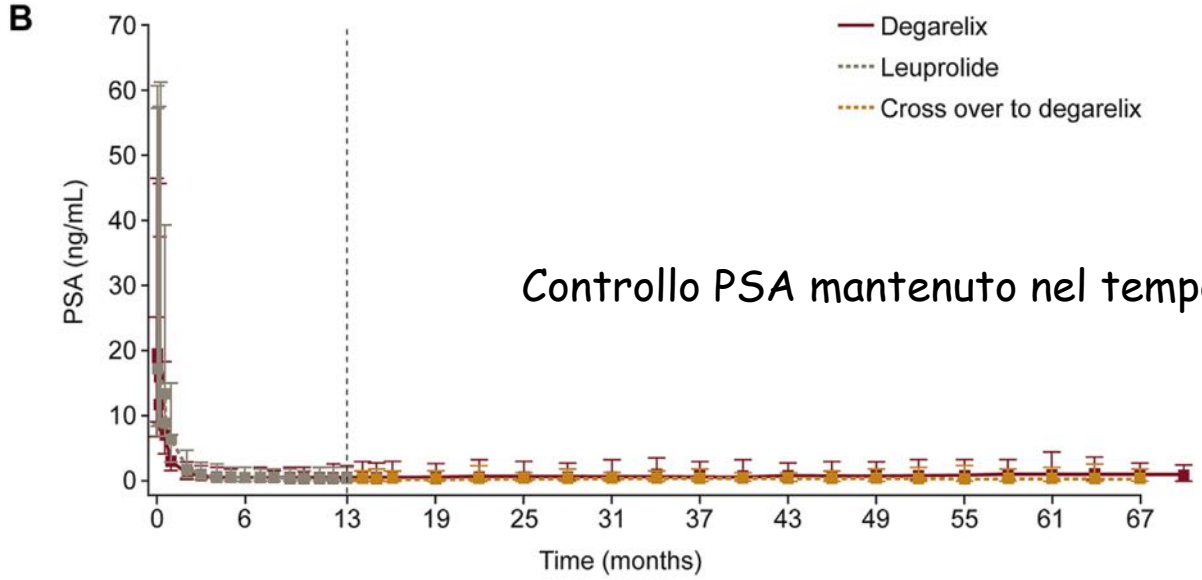
Klotz et al. BJU Int 2008;102:1531-1538

Direct comparative studies btw (ant)agonists



Effetti del T basale sulla soppressione di T nel lungo termine

Crawford ED et al., Urology, 83(5):1122-8,2014



Controllo PSA mantenuto nel tempo

Microsurges di T a seguito delle iniezioni

Microsurges di testosterone*			
Variazione: giorni 3 e 7 dopo la 9ª somministrazione	Degarelix 240➔160 mg	Degarelix 240➔80 mg	leuprorelina 7,5 mg
>0,25 ng/ml	0	0	8 (5%)*

*Aumento del testosterone >0,25 ng/ml rilevabile in 2 misurazioni qualsiasi a 3 e a 7 giorni dopo la somministrazione del farmaco

Klotz et al., BJU Int 2008;102:1531-1538

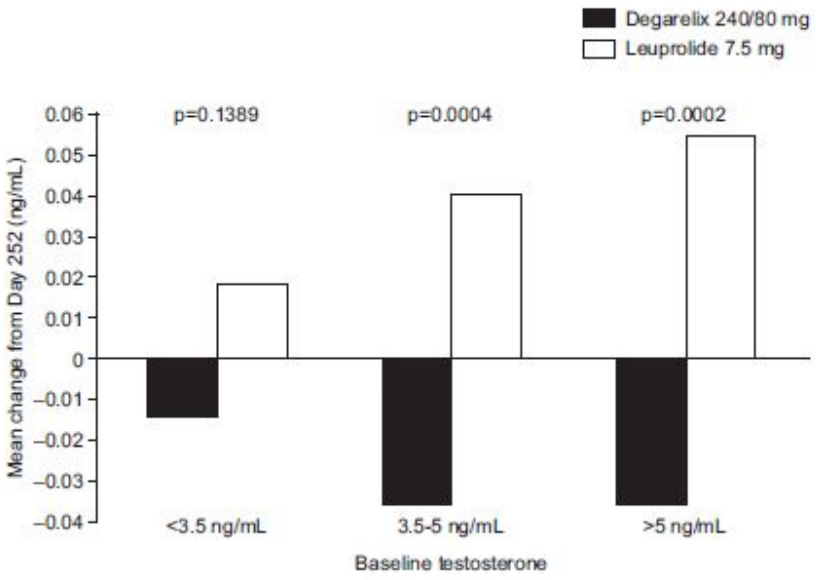


Figure 2. Mean changes in testosterone levels on day 255 compared with day 252.

Microsurges

Il 3° giorno dopo la nona somministrazione (g=255): con leuprorelina l'intensità del micropicco aumenta con l'aumentare del T basale

Damber JE et al. , Urology 2012; 80(1):174–181

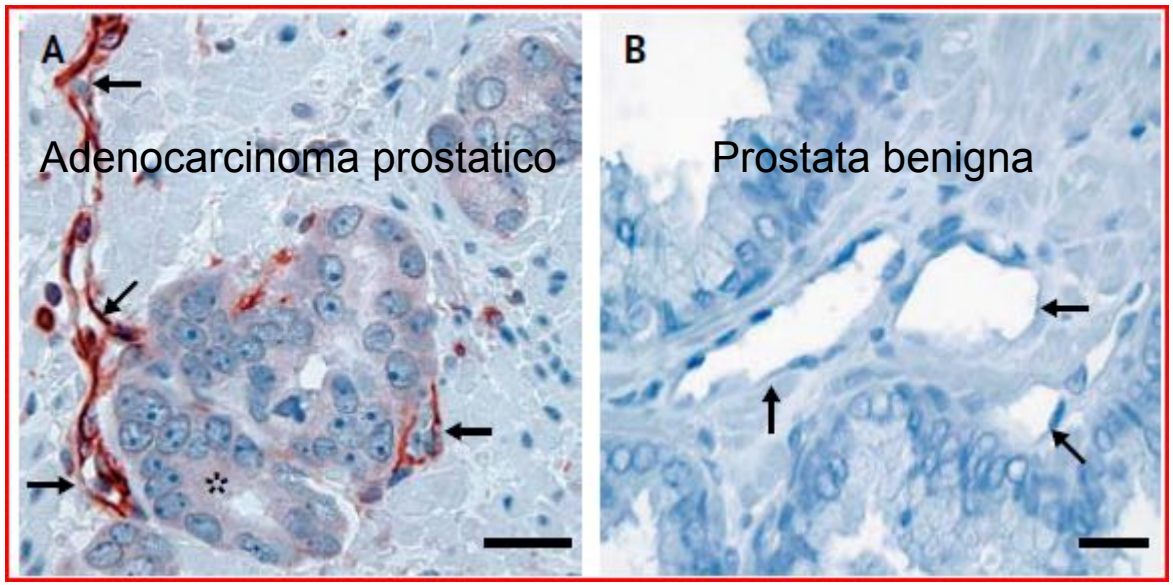
The NEW ENGLAND JOURNAL of MEDICINE

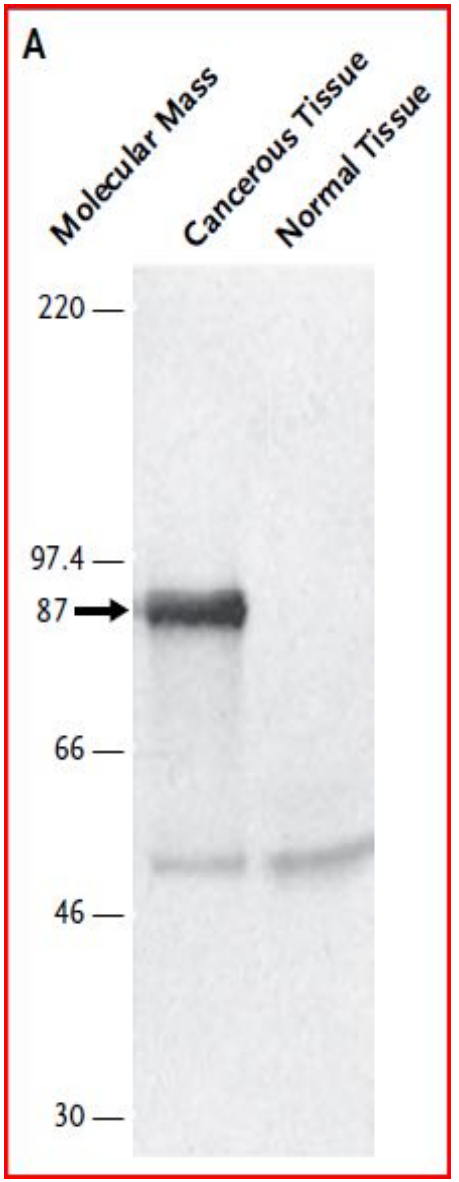
ORIGINAL ARTICLE

Expression of Follicle-Stimulating Hormone Receptor in Tumor Blood Vessels

Aurelian Radu, Ph.D., Christophe Pichon, Ph.D., Philippe Camparo, M.D., Martine Antoine, M.D., Yves Allory, M.D., Anne Couvelard, M.D., Gaëlle Fromont, M.D., Mai Thu Vu Hai, Ph.D., and Nicolae Ghinea, Ph.D.

N ENGL J MED 363;17 NEJM.ORG OCTOBER 21, 2010





- Il legame FSH/FSHR potrebbe indurre segnali angiogenetici mediati da VEGF/VEGFR in cellule endoteliali tumorali
- Il blocco del segnale FSH potrebbe essere una nuova strategia antitumorale

Azione su FSH

- Orchiectomia: ⇕
- GNRH agonisti: ⇓(circa 50% escape?)
- GnRH antagonisti: ⇓⇓

FSH stimola la crescita delle cellule tumorali prostatiche

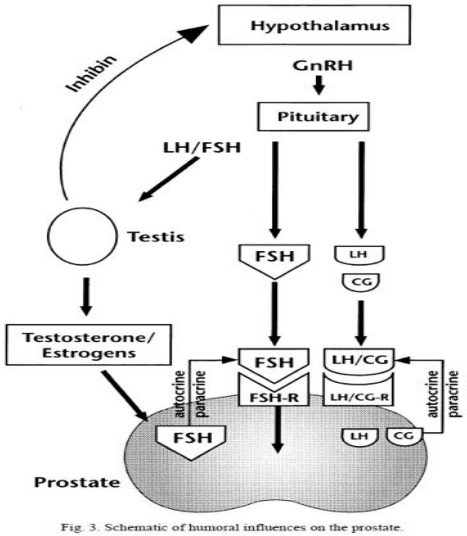
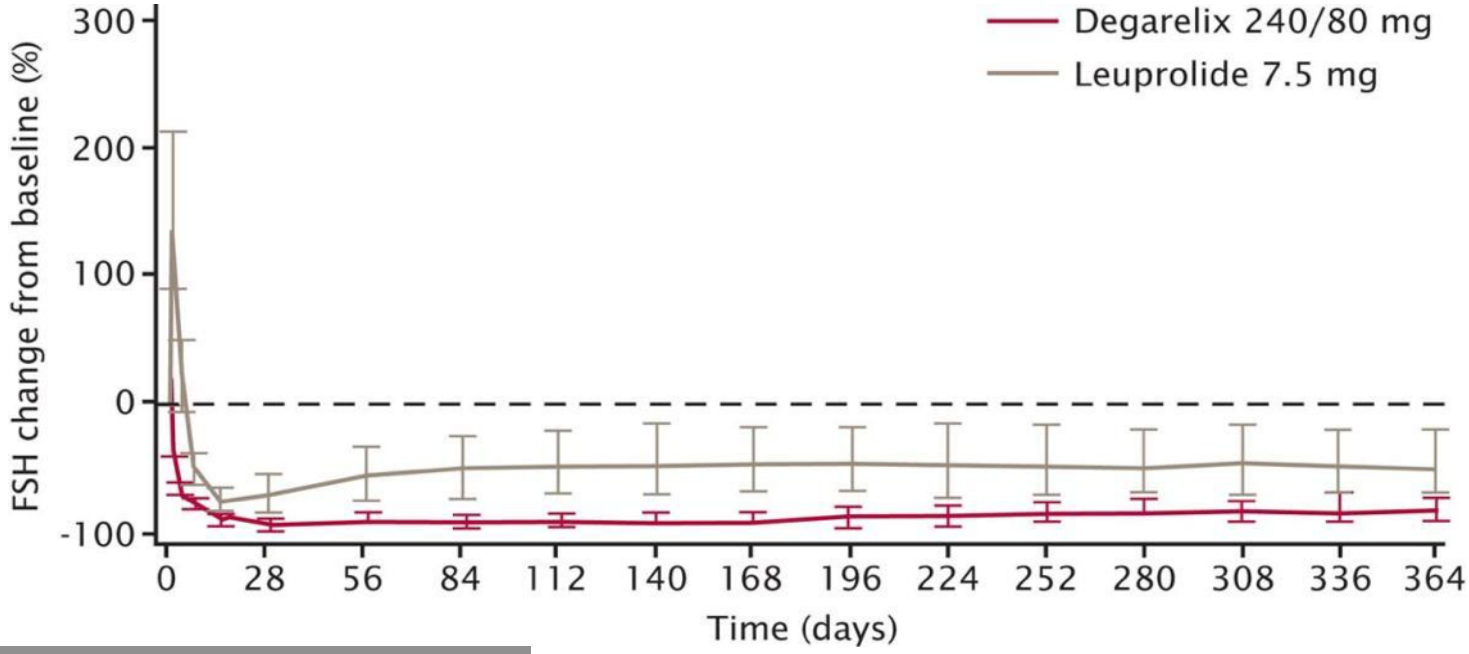


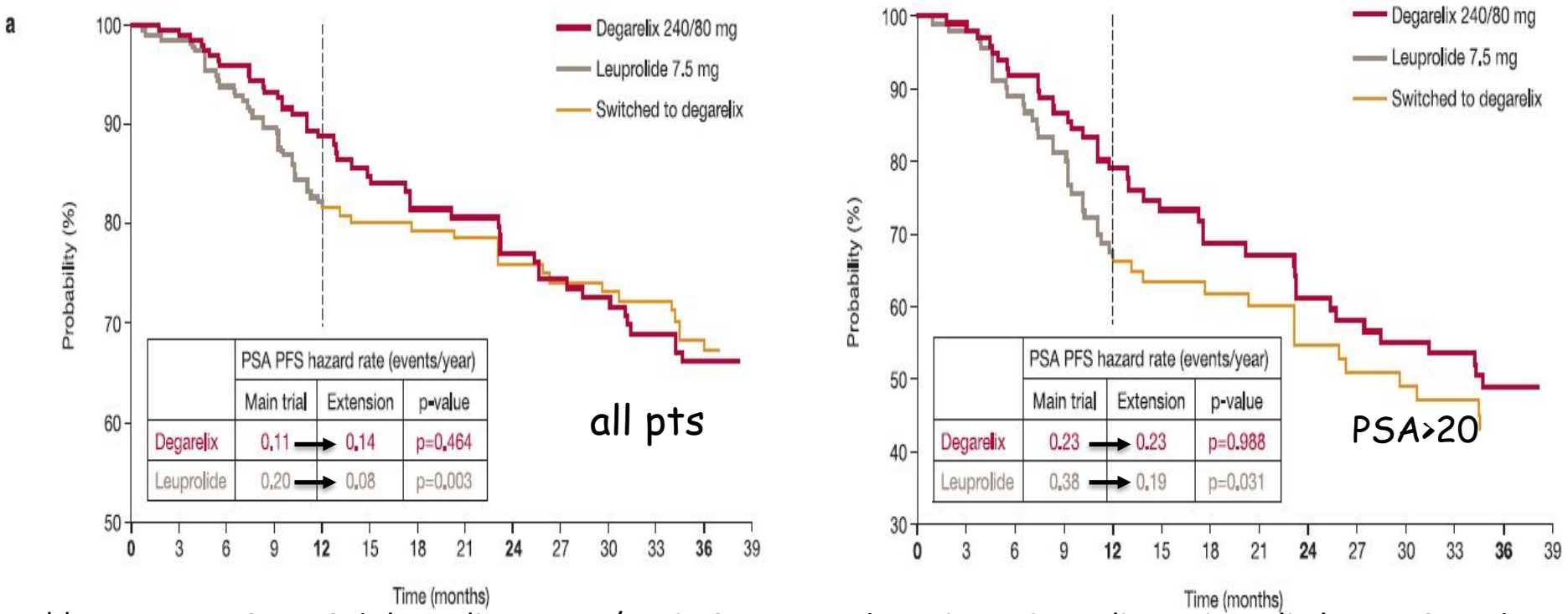
Fig. 3. Schematic of humoral influences on the prostate.



Klotz et al. BJU Int 2008;102:1531-1538

Which pts are most suitable for degarelix?

Sopravvivenza libera da progressione (tempo al PSA failure**/morte) dopo switch a degarelix



** aumento PSA ≥50% da nadir e ≥5 ng/mL in 2 consecutive misurazione distanziate di almeno 2 settimane

Time for 25% pts w baseline PSA>20 ng/ ml to experience PSA failure or death significantly longer w degarelix (514 vs 313d)

Crawford ED et al., Urology, 83(5):1122-8,2014

Which pts are most suitable for degarelix?

ADT for downsizing

Original article

Neoadjuvant androgen deprivation for prostate volume reduction: The optimal duration in prostate cancer radiotherapy

Johan F. Langenhuijsen, M.D.[a,*], Emile N. van Lin, M.D., Ph.D.[b], Aswin L. Hoffmann, M.Sc.[b], Ilse Spitters-Post, B.Sc.[b], J. Alfred Witjes, M.D., Ph.D.[a], Johannes H. Kaanders, M.D., Ph.D.[b], Peter F. Mulders, M.D., Ph.D.[a]

[a] *Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*
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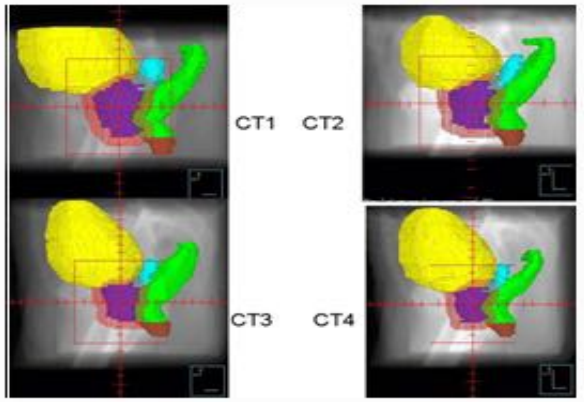
Received 29 December 2008; received in revised form 30 March 2009; accepted 31 March 2009

Urol Oncol, 2010,



Prostate volume reduction (purple) shown on sagital plane of CT scans; CT1 = baseline; CT2 = after 3 months of MAB; CT3 = after 6 months of MAB; CT4 = after 9 months of MAB. (Color version of figure is available online.)

- Volume reduction: 30-60%
- > apopthosis, > radiosensitation (> blood flow/<hypoxia)
- Better effect when prostate volume > 60cc
- TIMING:3-6 months

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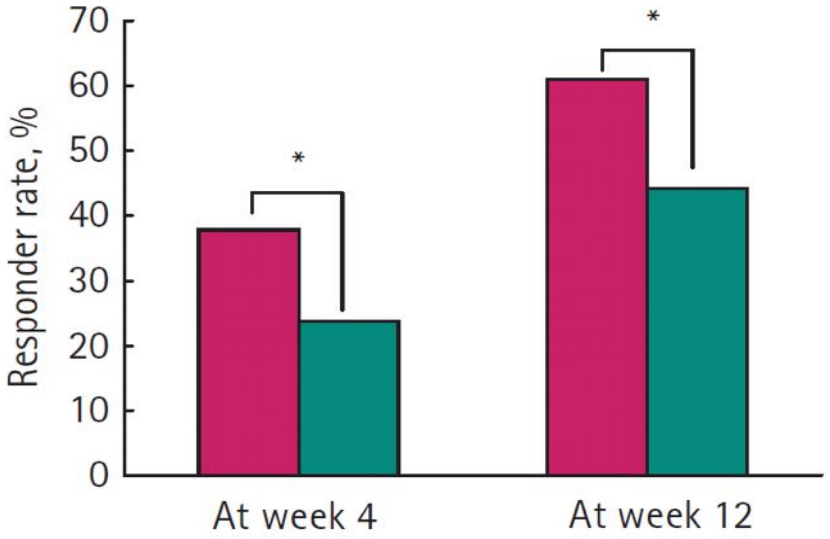
Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide

Karol Axcrona[1], Sirpa Aaltomaa[2], Carlos Martins da Silva[3], Haluk Özen[4], Jan-Erik Damber[5], László B. Tankó[6], Enrico Colli[6] and Peter Klarskov[7]

- TPV ridotto significativamente in entrambi i gruppi: **-37,2%** con degarelix e **-39%** con goserelin

- % pazienti con sollievo dei sintomi significativo (almeno 3 punti) maggiore con degarelix (61%) rispetto a goserelin (44,3%) p=0,02



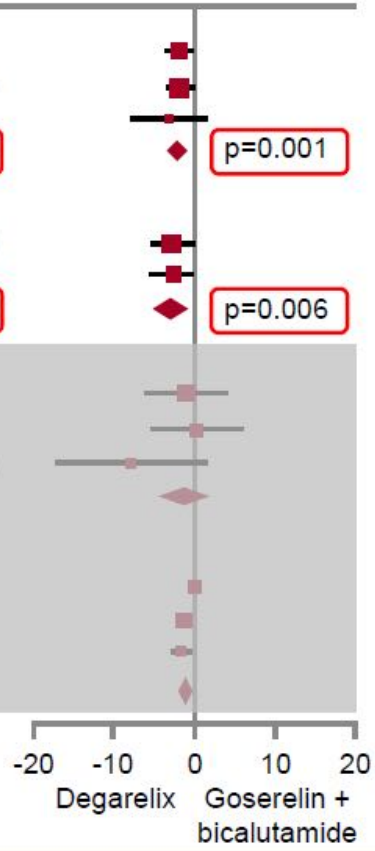
Urologia Internationalis

Original Paper

Degarelix versus Goserelin plus Bicalutamide Therapy for Lower Urinary Tract Symptom Relief, Prostate Volume Reduction and Quality of Life Improvement in Men with Prostate Cancer:

LUTS relief: A meta-analysis of trials comparing degarelix with LHRH agonists

Study or subgroup (first author)	Degarelix			Goserelin plus bicalutamide			Mean difference IV, fixed, 95% CI
	Mean	SD	n	Mean	SD	n	
IPSS							
Axcrona	**-4.4**	6.3	82	**-2.7**	5.9	97	-1.70 (-3.50, 0.10)
Mason	-1.71	5.6	180	0.11	5.2	64	-1.82 (-3.33, -0.31)
Anderson	-11.6	6.8	27	-8.6	6.9	13	-3.00 (-7.54, 1.54)
Total (95% CI)			289			174	-1.85 (-2.97, -0.72)
IPSS ≥13							
Axcrona	-6.73	6.1	52	-4.02	7.2	55	-2.71 (-5.23, -0.19)
Mason	-6.04	5.8	53	-3.41	5.1	17	-2.63 (-5.51, 0.25)
Total (95% CI)			105			72	-2.68 (-4.57, -0.78)
TPV							
Axcrona	-20.4	16.3	82	-19.5	17.7	97	-0.90 (-5.89, 4.09)
Mason	-18.3	20.3	180	-18.5	18.8	64	0.20 (-5.28, 5.68)
Anderson	-21.8	14.0	27	-14.0	14	13	-7.80 (-17.06, 1.46)
Total (95% CI)			289			174	-1.41 (-4.84, 2.01)
QoL related to urinary symptoms							
Axcrona	-1.29	1.6	82	-1.27	1.7	97	-0.02 (-0.50, 0.46)
Mason	-0.76	1.6	180	0.16	1.6	64	-0.92 (-1.38, -0.46)
Anderson	-1.8	1.6	27	-0.6	1.8	13	-1.20 (-2.35, -0.05)
Total (95% CI)			289			174	-0.63 (-1.36, 0.10)



Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them

Paul L. Nguyen [a,], Shabbir M.H. Alibhai [b], Shehzad Basaria [c], Anthony V. D'Amico [a], Philip W. Kantoff [d], Nancy L. Keating [e], David F. Penson [f], Derek J. Rosario [g], Bertrand Tombal [h], Matthew R. Smith [i]*

Summary of evidence-based strategies to reduce androgen deprivation therapy side effects

Side effect	Evidence-based strategies to reduce effects	References
Decreased bone health	Calcium (1000–1200 mg daily from diet and supplements)	[14]
	Vitamin D (800–1000 IU daily)	[14]
	For men with FRAX risk of hip fracture >3%:	
	• Denosumab (increased BMD and decreased fractures)	[21]
	• Zoledronic acid (increased BMD, alternative if denosumab not available)	[17,20,27]
	• Alendronate (increased BMD, alternative if denosumab not available)	[18,19]
Metabolic consequences	Exercise (aerobic and resistance)	[39–41,43,44]
	ATP III and AHA/ACC guidelines for lipids	[36,47]
Increased diabetic risk	ADA guidelines for screening high-risk patients	[45,46]
	Closer monitoring of control among those with preexisting diabetes	
Cardiovascular events	–	
Sexual dysfunction	Intermittent ADT for rising PSA after radiation	[73]
	Use shortest acceptable duration of ADT	[76]
Gynecomastia	Prophylactic radiation	[78,80]
	Prophylactic tamoxifen	[81,82]
Reduced penile/testis size	–	
Fatigue	Exercise (aerobic and resistance)	[87–91]
Hot flashes	Medroxyprogesterone	[93]
	Venlafaxine	[93]
	Gabapentin	[92]
Cognitive changes	–	
Anemia	–	

ADA = American Diabetes Association; ADT = androgen-deprivation therapy; AHA/ACC = American Heart Association/American College of Cardiology; ATP III = Adult Treatment Panel III; BMD = bone mineral density; FRAX = World Health Organization Fracture Risk Assessment Tool; PSA = prostate-specific antigen.

ADT toxicity

- Hot flushes : 50-80% pts

- Metabolic effects: >50% pts
  - weight gain
  - lipids
  - insulin resistance

  Cardiovascular : increased risk from 19% to 24%
  (monitoring of pressure, lipid profile, glucose level)

- Muscoloskeletal:
  - muscle loss and weakness
  - osteoporosis/osteopenia (increased risk of fracture up to 19%)

- Fatigue (40% pts receiving long term ADT)

ADT toxicity

- Neurocognitive: memory (conflicted results)
  depression (+ 7-8%)
- Anaemia (normocytic normocromic)
- Hepatotoxicity : AA
- Sexual : -loss of libido (up to 95% pts)
  - decreased penile and testicle size,
  - thinning of body hair
  - erectile disfunction
  - gynecomastia and breast pain (AA- up to 85%pts)

Screening, detection and management of ADT toxicities

ADT toxicity

- **Testosterone flare up**: 10% MTS pts

  initial testosterone surge w LHRH agonists if given w/o AA cover. Flare up can result in spinal cord compression,severe bone pain, bladder outlet obstruction, obstructive ranal failure, hypercoagulation state (AA cover , LHRH antagonists)

- **Reactions at the injection sites:** 40% pts LHRH-antagonists

---

- **Abiraterone** : Mineralcorticoid effects - oedema , hypokaliemia ,

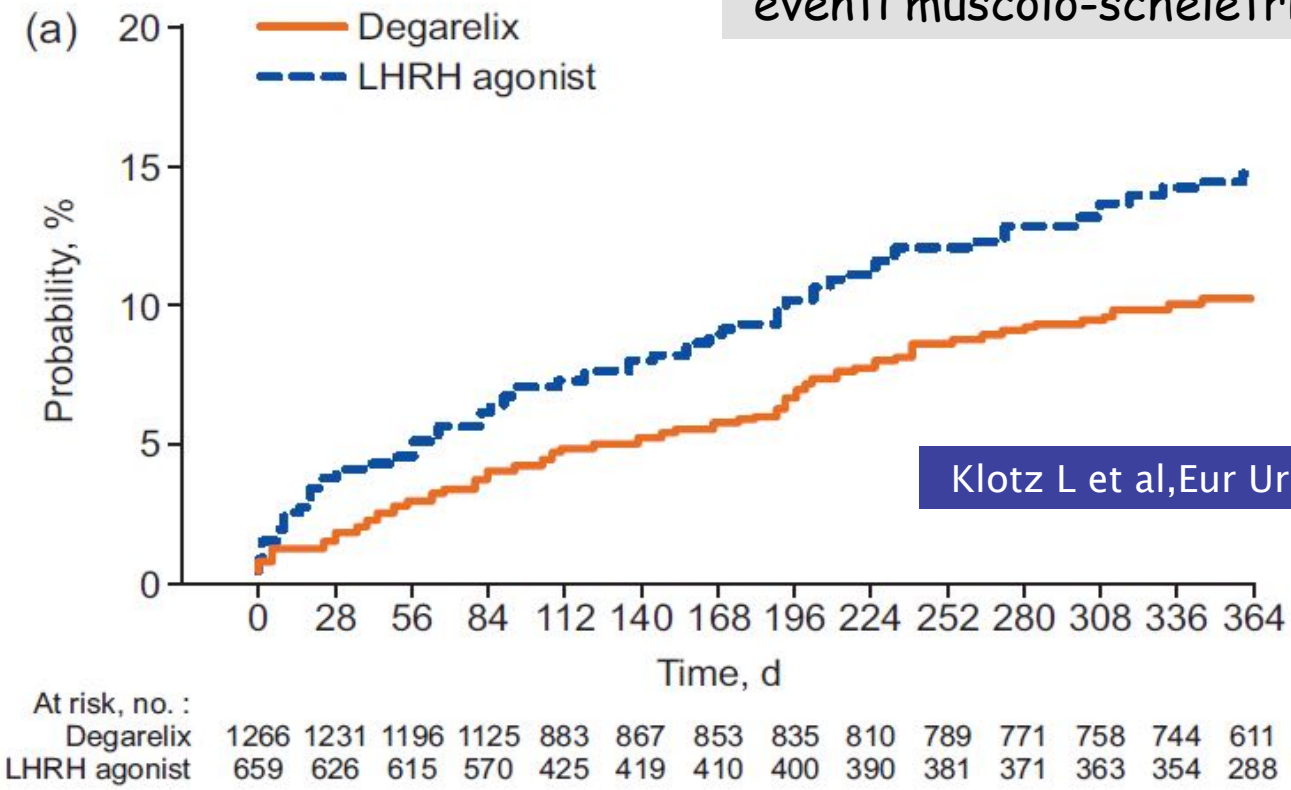
- **Enzalutamide** : fatigue (34%),diarrhoea (21%), hot flushes (20%), muscoloskeletal pain (14%), headache (12%) ; pts with seizures excluded

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists

Q1 *Laurence Klotz [a,*], Kurt Miller [b], E. David Crawford [c], Neal Shore [d], Bertrand Tombal [e], Cathrina Karup [f], Anders Malmberg [f], Bo-Eric Persson [g]*

eventi muscolo-scheletrici



Klotz L et al,Eur Urol, 2014

Biochemical and Biophysical Research Communications 422 (2012) 54–58

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Blocking FSH action attenuates osteoclastogenesis

Ling-Ling Zhu [a,b], Irina Tourkova [c,d], Tony Yuen [b], Lisa J. Robinson [c,d], Zhuan Bian [a], Mone Zaidi [b,*,1], Harry C. Blair [c,d,e,*,1]

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Short Communication

Follicle-stimulating hormone promotes RANK expression on human monocytes

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The Effects of Androgen Deprivation Therapy on Cardiac Function and Heart Failure: Implications for Management of Prostate Cancer

Scott Edelman,[1,2] Javed Butler,[3] Bruce W. Hershatter,[1,2] Mohammad K. Khan[1,2]

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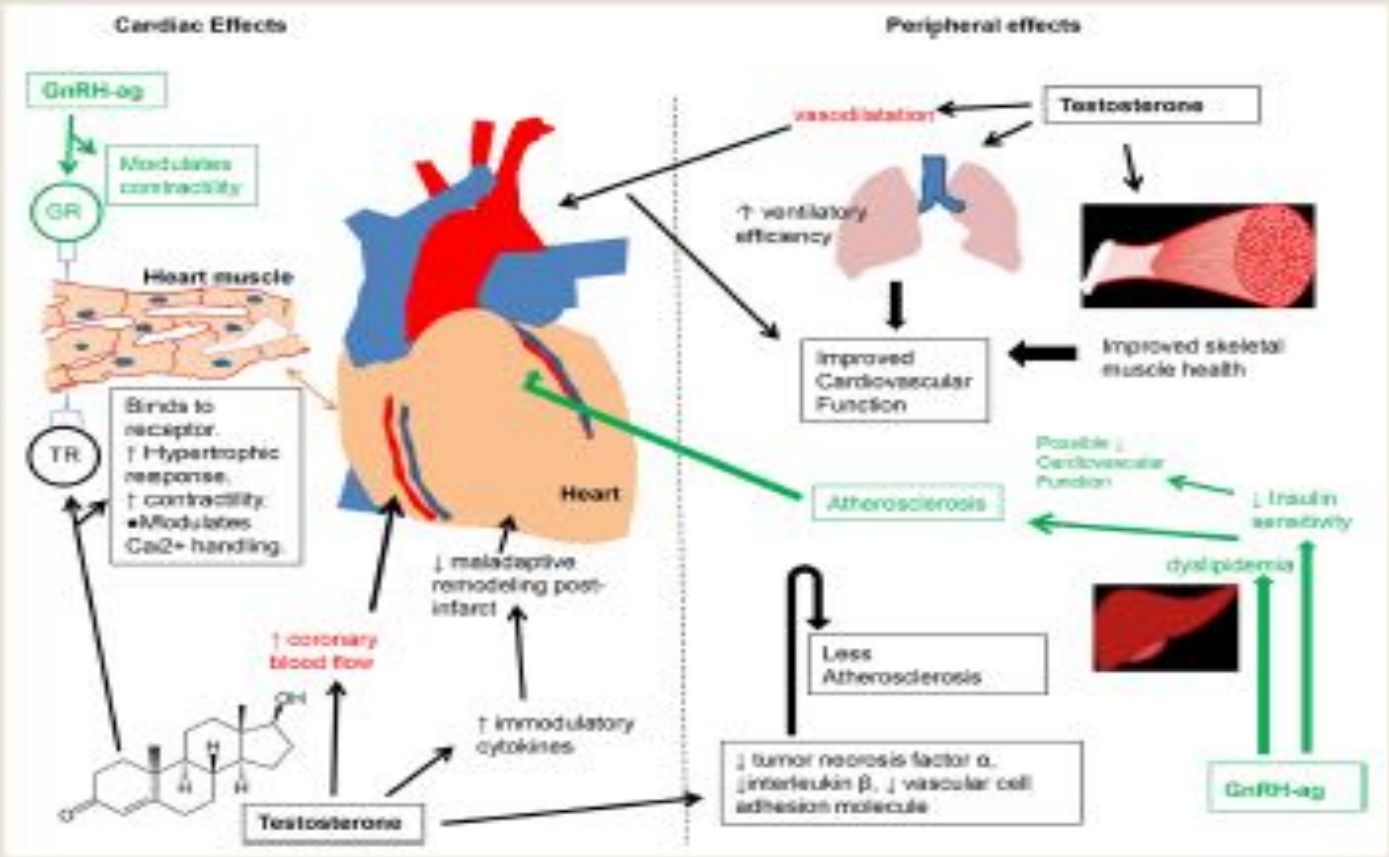
Figure 1 Cardiac and Peripheral Effects



Cardiovascular harm: a controversial issue

- SEER Medicare study (Keating , JCO, 2006)
  .. incresead risk of coronary heart disease, MI and sudden cardiac death among men receiving ADT (Gn-RH agonist) ..

- CaPSURE Registry (Tsai, J Natl Cancer Inst, 2007)
  ..in men > 65 yrs, receiving RP and also received ADT higher risk of fatal CV events..

- Dana-Farber 95-096/TROG 96.01 (D'Amico, JCO, 2007) .. .. Among the men > 65 yrs, 6 months of ADT resulted in a significantly shorter time to fatal MI,although total n^ of cardiac events by 7 yrs are the same..

AHA/ACS/AUA Science Advisory

Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology.

Levine et al. Circulation 2010;121:833-840

… at this point, it is reasonable on the basis of the above data, to state that there may be a relation btw ADT and cardiovascular events and death…

Cardiovascular harm: a controversial issue

- Ontario case-control study (Alibhai, JCO, 2009)
  .. data related to 20.000 men, didn't find ADT to be associated w acute MI or sudden cardiac death..

- CaPSURE reanalisys-propensity matching (Punnen, JCO, 2011)
  no association

- RTOG 85-31 reanalysis (Efsthatiou, J CO, 2009)
- RTOG 86-10 reanalysis (Roach III, JCO,2008)
- TROG 96.01 reanalysis (Wilcox , Oncology, 2008)
- RTOG 92-02 reanalysis (Efsthatiou , Eur Urol, 2008)
- Metanalysis of 11 RCTs (Nguyen, JAMA, 2011)
  no association

Cardiovascular harm: baseline comorbidity

- BUT.....many of the pts in the control arm eventually received ADT, trials are not powered to detect a difference in CV mortality or outcomes, metanalysis was not able to stratify by baseline comorbidity

- ADT use was associated w > mortality only among patients who had a priori MI or diagnosis of CHF (Nanda,JAMA,2009)
- Increased risk of mortality w ADT in men with CHF or prior MI for men wihth high risk prostate cancer (Nguyen,IJROBP,2012)
- SEER-Medicare:..baseline comorbidity didn't modify the impact of ADT on the risk of MI.. (Keating, Eur Urol, 2013)

The impact of androgen-deprivation therapy (ADT) on the risk of cardiovascular (CV) events in patients with non-metastatic prostate cancer: a population-based study

BJUI
BJU International

Giorgio Gandaglia*†, Maxine Sun*, Ioana Popa*‡, Jonas Schiffmann*§, Firas Abdollah†, Quoc-Dien Trinh¶, Fred Saad‡, Markus Graefen§, Alberto Briganti†, Francesco Montorsi† and Pierre I. Karakiewicz*‡

- Studio retrospettivo su 140.474 uomini con CaP non-metastatico;
- Confronto di GnRH-agonisti vs orchiectomia bilaterale vs nessuna terapia androgenica;(esclusi pazienti con morbidità CV)

- End Point cardiovascolari: Malattie coronariche (CAD), infarto del miocardio (AMI), morte cardiaca improvvisa (SCD).

RISULTATI:

- GnRH-agonisti sono associati con un aumento di rischio di CAD, AMI, SCD rispetto al non trattato e all'orchiectomia.
- ADT alternative dovrebbero essere considerate in pazienti con un alto rischio di eventi cardiovascolari.

Cardiovascular harm: a controversial issue

To summarize:

- Available data suggest that ADT results in unfavorable metabolic changes and may increase the risk for CV events, although most studies report that ADT is not linked to greater CV mortality

- Need for Identification of pts at risk, , more tailoring of the form and duration of ADT, better monitoring and management of the CV risk factors.

  Lester JF, Lason MD, Drug,Healthcare and Patient safety, 2015

- Currently, the best way to limit the CV harms of ADT is to avoiding it in pts who don't need it or using alternatives to GnRH agonists in men with pre-existing CV disease (orchiectomy, GnRH antagonists).

  Nguyen PL et al, Eur Urol, 2015

Cardiovascular harm: LHRH (anta)agonists

- No significant difference btw in CV events w 1 yr leuprolide vs degarelix - RCT

  Smith MR et al , J Urol, 2010

- Rate of CV similar before and after administration of degarelix, (although event rate higher after degarelix in pts w baseline CV disease) – pooled analisys

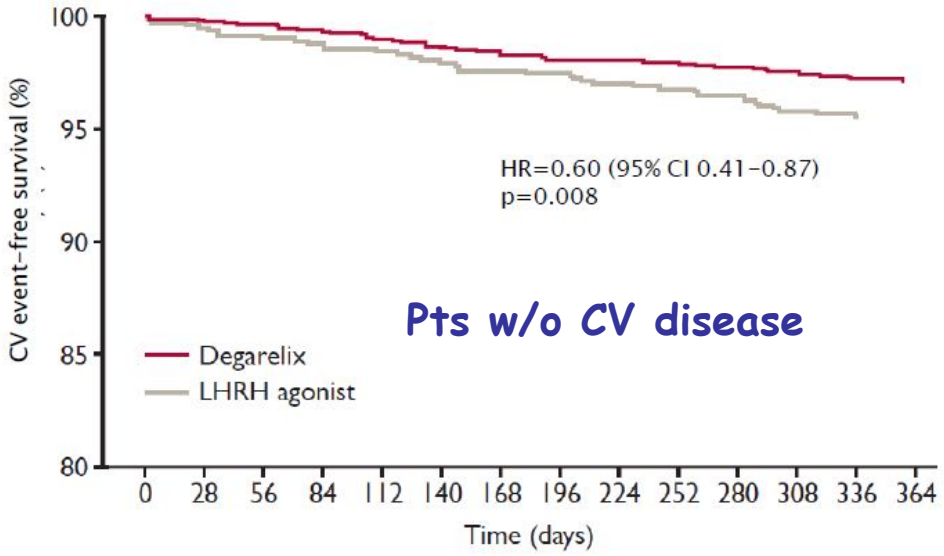
  Smith MR et al , J Urol, 2011

- Degarelix associated w lower risk of CV events than leuprolide, particularly in pts w baseline CV disease (but not in men w /o history of CV disease - pooled analisys from 6 RCT trials

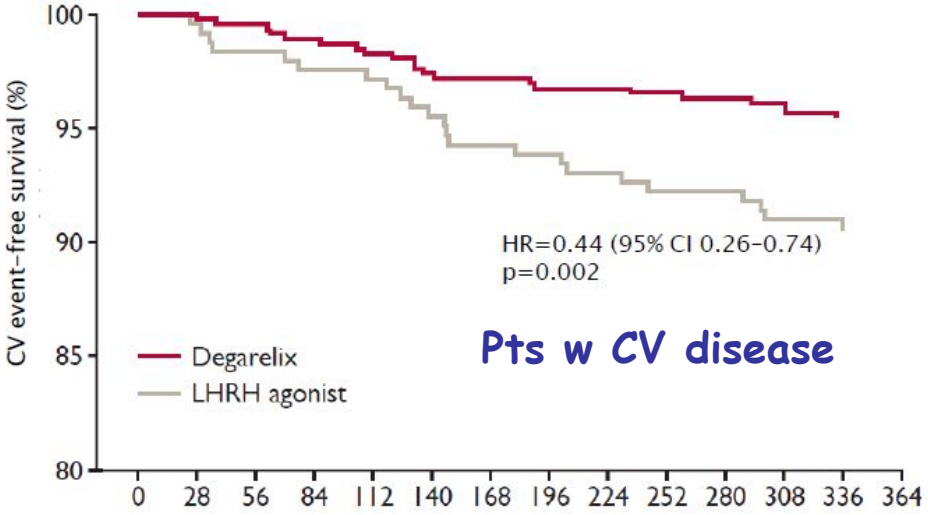
  Albertsen PC et al, Eur Urol, 2014

Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist

Peter C. Albertsen[a,*]



Pts w/o CV disease



Pts w CV disease

Table 2 – Baseline characteristics of the two treatment groups

Variable	GnRH antagonist (n = 1491)	GnRH agonist (n = 837)
Age, yr (range)	71.7 (46–94)	71.6 (51–98)
Body mass index	27.2	27.5
Body mass index >30, % (no.)	22.4 (334)	23.9 (200)
History of cardiovascular disease, % (no.)	31.1 (463)	29.3 (245)
History of smoking, % (no.)	47.4 (707)	51.6 (432)
History of alcohol use, % (no.)	59.6 (889)	56.8 (475)
History of hypertension, % (no.)	74.9 (1117)	73.5 (615)
Serum cholesterol level >6.2 mmol/l, % (no.)	26.8 (399)	29.5 (247)
Statin medication use, % (no.)	26.8 (400)	28.0 (234)
History of diabetes, % (no.)	14.8 (221)	15.3 (128)

GnRH = gonadatropin-releasing hormone.

Clinical recommendations for adapting the use of ADT for prostate cancer in men with or at risk for Congestive Heart Failure

Population	Recommandationfs for ADT
MTS, Smptomatic	GNRH-ag mainstay, IAT might be considered.
MTS, Asymptomatic	GNRH-ag mainstay, in carefully , in selected pts consider AS. IAT might be considered.
BiochFailure after RT	Consider deferring ADT and/or IAT.
High risk localized cancer	-Consider reducing AA duration to 3-4 wks (not MAB) -For PSA>20 ng/ml,stage<T2b, GS 3+3 consider omitting ADT ; for stage <T2b, consider 6 mo of ADT -For stage >T2c consider an intermediate duration of ADT btw 6 mo and 2 yrs
Intermediate risk	Consider withholding ADT

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OT intermittente

Original Investigation

Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer
A Systematic Review and Meta-analysis

Magnan et al., JAMA Oncol., 2015

Sindy Magnan, MD, MSc, FRCPC; Ryan Zarychanski, MD, MSc, FRCPC; Laurie Pilote, MD; Laurence Bernier, MD; Michèle Shemilt, MSc; Eric Vigneault, MD, MSc, FRCPC; Vincent Fradet, MD, PhD, FRCSC; Alexis F. Turgeon, MD, MSc, FRCPC

CONCLUSIONS AND RELEVANCE Intermittent androgen deprivation was not inferior to continuous therapy with respect to the overall survival. Some quality-of-life criteria seemed improved with intermittent therapy. Intermittent androgen deprivation can be considered as an alternative option in patients with recurrent or metastatic prostate cancer.

Degarelix as an Intermittent Androgen Deprivation Therapy for One or More Treatment Cycles in Patients with Prostate Cancer

Laurent Boccon-Gibod [a], Peter Albers [b], Juan Morote [c], Hendrik van Poppel [d], Jean de la Rosette [e], Arnauld Villers [f], Anders Malmberg [g], Anders Neijber [h], Francesco Montorsi [i,]*

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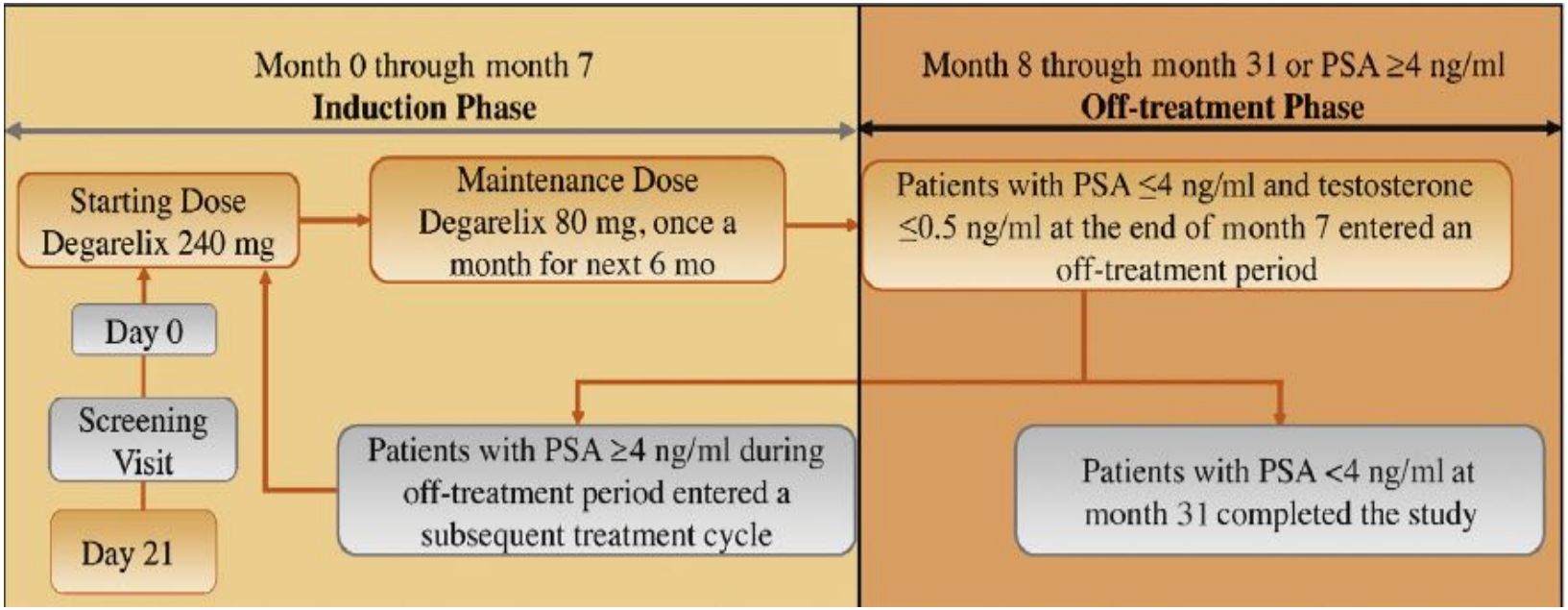
EUROPEAN UROLOGY 66 (2014) 655–663

DISEGNO DELLO STUDIO

- Studio in aperto a singolo braccio con un massimo di 3 cicli di terapia
- Pazienti loc avanzati e metastatici, 4 ng/ml<PSA≤50ng/ml o pazienti trattati con intento curativo e con PSA DT<24 mesi e PSA≤ 50ng/ml ECOG ≤2, aspettativa vita ≥ 24 mesi



Results and limitations: Of 213 patients in the first induction period, 191 entered the first offtreatment period, 35 patients entered the second induction, and 30 entered the second offtreatment period. Only two patients entered the third cycle. **Median time to PSA >4 ng/ml and duration of first off-treatment period was 392 d each**. Significant differences in time to PSA >4 ng/ml were observed between subgroups stratified by prognostic factors (previous curative treatment, cancer stage, PSA levels, and Gleason scores). **Time to testosterone >0.5 and >2.2 ng/ml was 112 and 168 d, respectively. Change in QoL remained non significant, and sexual function gradually improved during the off-treatment period**. Adverse events were fewer during the offtreatment period and subsequent treatment cycles.
Conclusions: **IAD with degarelix resulted in an improvement in sexual function commensurate with increased testosterone levels while PSA remained suppressed**. The treatment for one treatment cycle or more was well tolerated.

Tempo a PSA >4ng/ml nel ciclo 1: 392 gg
Tempo a PSA >4ng/ml nel ciclo 2: 224 gg

Tempo a Testosterone>0.5 ng/ml nel ciclo 1: 112 gg
Tempo a Testosterone>2.2 ng/ml nel ciclo 1: 168 gg
Tempo a Testosterone> 3ng/ml nel ciclo 1: 224 gg
Dati simili sono stati osservati nel secondo ciclo

Summary

- ADT is the mainstay of treatment for locally advanced (+RT) and metastatic PCa.
- GnRh agonists are the standard of care.
- More recently, GNRH antagonists have been developed as a new class of ADT, offering potential advantages related to their mechanism of action.
- GnRH antagonist degarelix suppresses testosterone and PSA more rapidly with no testosterone surge or subsequent microsurge; faster castration onset may benefit pts presenting with critical clinical problems ; emerging role for neoadiuvant/downsizing and intermittent ADT.

Summary

- For men at risk for cardiovascular disease who are receiving ADT, AHA issued an advisory for evaluation and monitoring the risk factors involved and for better identification of pts at risk.
- In such a pts we must individualize the risk benefit-ratio and the optimal length of ADT.
- Side effects such as cardiovascular and mucoloskeletal events appear to be reduced in antagonists.
- The overall benefit/risk profile of degarelix supports its use as alternative in first line of ADT, specially in those w cardiovascular risk.