Hormone therapy in prostate cancer - overview

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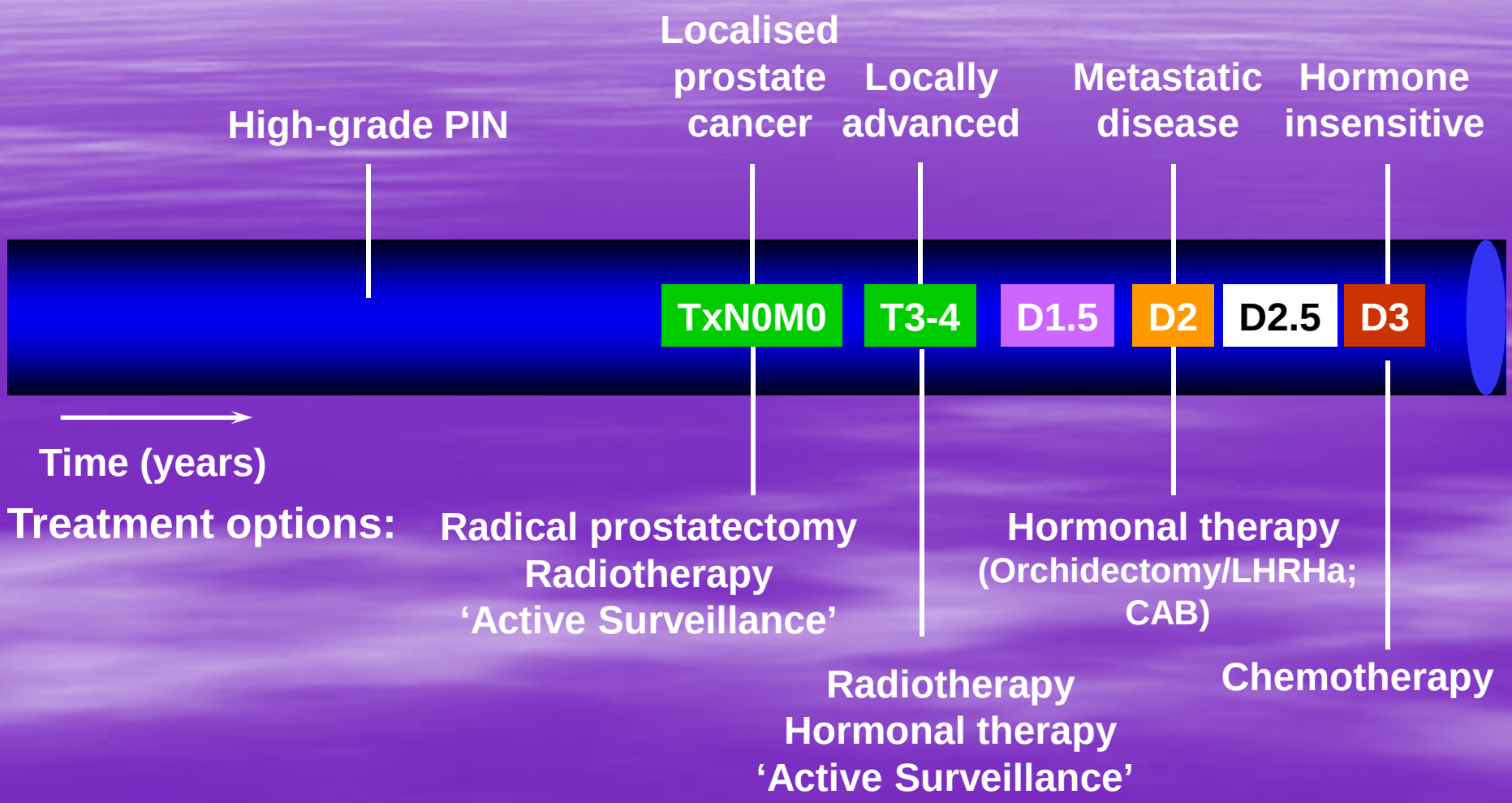
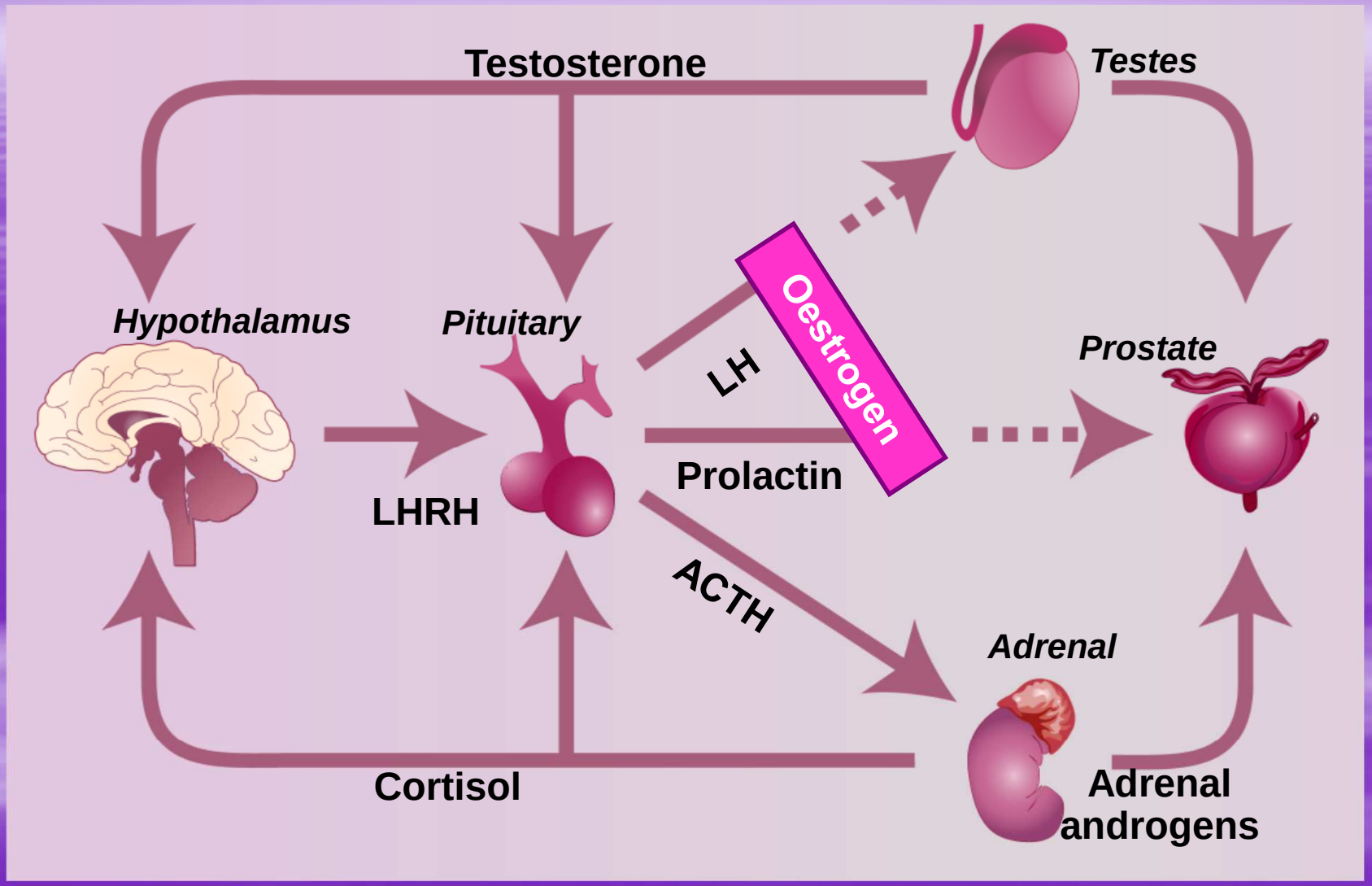
Prostate cancer and treatment options



PIN, prostatic intraepithelial neoplasia

Hormonal Therapy Options

Prostate cancer is hormone-dependent



LHRH, luteinising hormone-releasing hormone
LH, luteinising hormone
ACTH, adrenocorticotrophin

Hormonal Therapy

- Bilateral orchiectomy
- LHRH analogs
- Antiandrogens
- Combined Androgen Blockade (CAB)

Bilateral Orchiectomy

- In 1941, Huggins and Hodges made original discovery of hormonal effect on prostate cancer
- Same studies also showed that bilateral orchiectomy improved pain or neurological symptoms in 71% of patients with metastatic disease
- Advantages:
  - Immediate castration without testosterone surge
  - Outpatient procedure, general anesthesia not required
  - No compliance issues
- Disadvantages:
  - Irreversible

Huggins C, Hodges CV. *Cancer Res*. 1941;1:293-7.
Huggins C, et al. *Arch Surgery*. 1941;43:209.
Schroder FH. *Campbell's Urology,* 8th ed. Philadelphia, Pa. WB Saunders;2002:3190-91.

Hormonal Therapy in Metastatic Disease

- HT has been most widely used in metastatic disease
- When to initiate HT is often debated
- MRC (UK) Study
  - 938 patients with locally advanced and asymptomatic, metastatic prostate cancer
  - Early HT (89% orchiectomy; within 6 weeks of entry) vs Deferred HT (71.5% orchiectomy)
- Survival, local and distant progression, major complications evaluated

MRC Prostate Cancer Working Group Party Investigators Group *Br J Urol.* 1997;79:235-246.

MRC Trial: Results

- 934 evaluable patients results

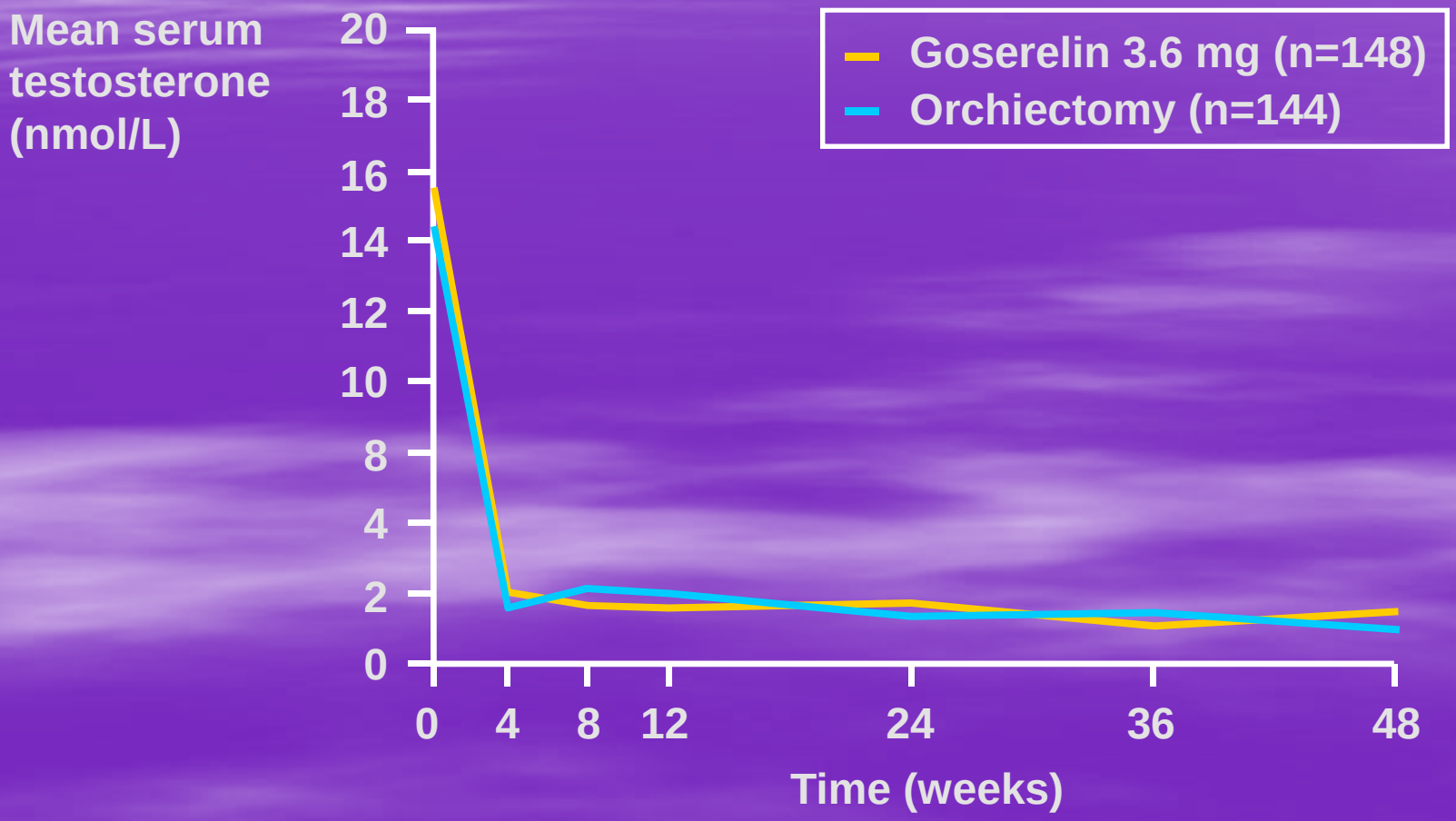
	Deferred ARM (# of patients)	Immediate ARM (# of patients)	P values
Death	361	328	P=0.02 Two-tailed
Cause Specific Death	257	203	P=0.001 Two-tailed
TUR	141	65	P<0.001 Two-tailed

MRC Prostate Cancer Working Group Party Investigators Group *Br J Urol.* 1997;79:235-246.

Castration alone in advanced disease

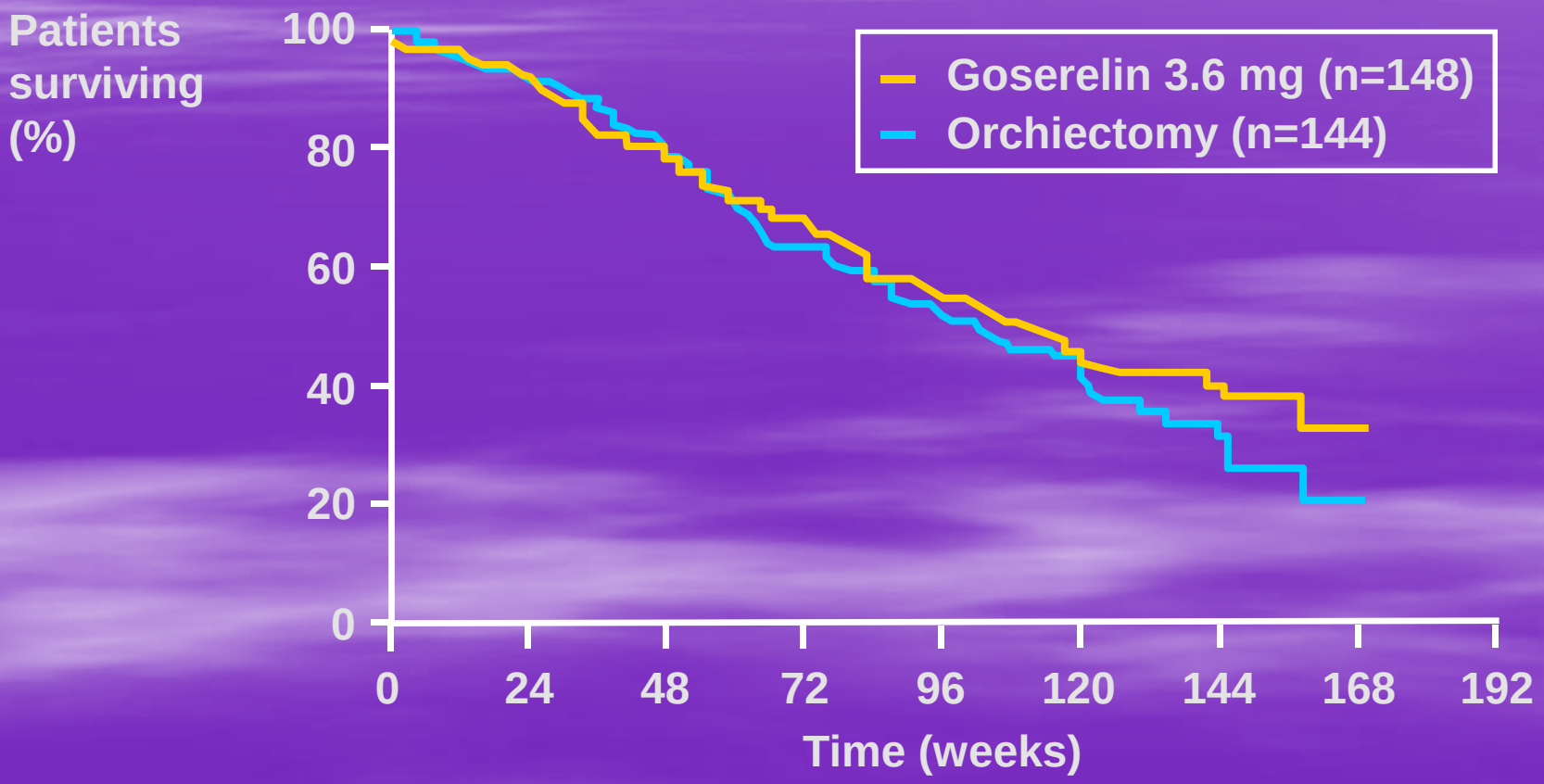
- Of all hormone-sensitive cancers, prostate cancer is the most sensitive to endocrine therapy
- Castration has been the ‘gold standard’ for treatment of advanced disease
- Surgical orchiectomy vs medical castration

Similar mean serum testosterone concentrations achieved with Zoladex (goserelin) 3.6 mg vs orchiectomy



Adapted from Peeling 1987

Zoladex 3.6 mg is as effective as orchiectomy in terms of overall survival in metastatic disease



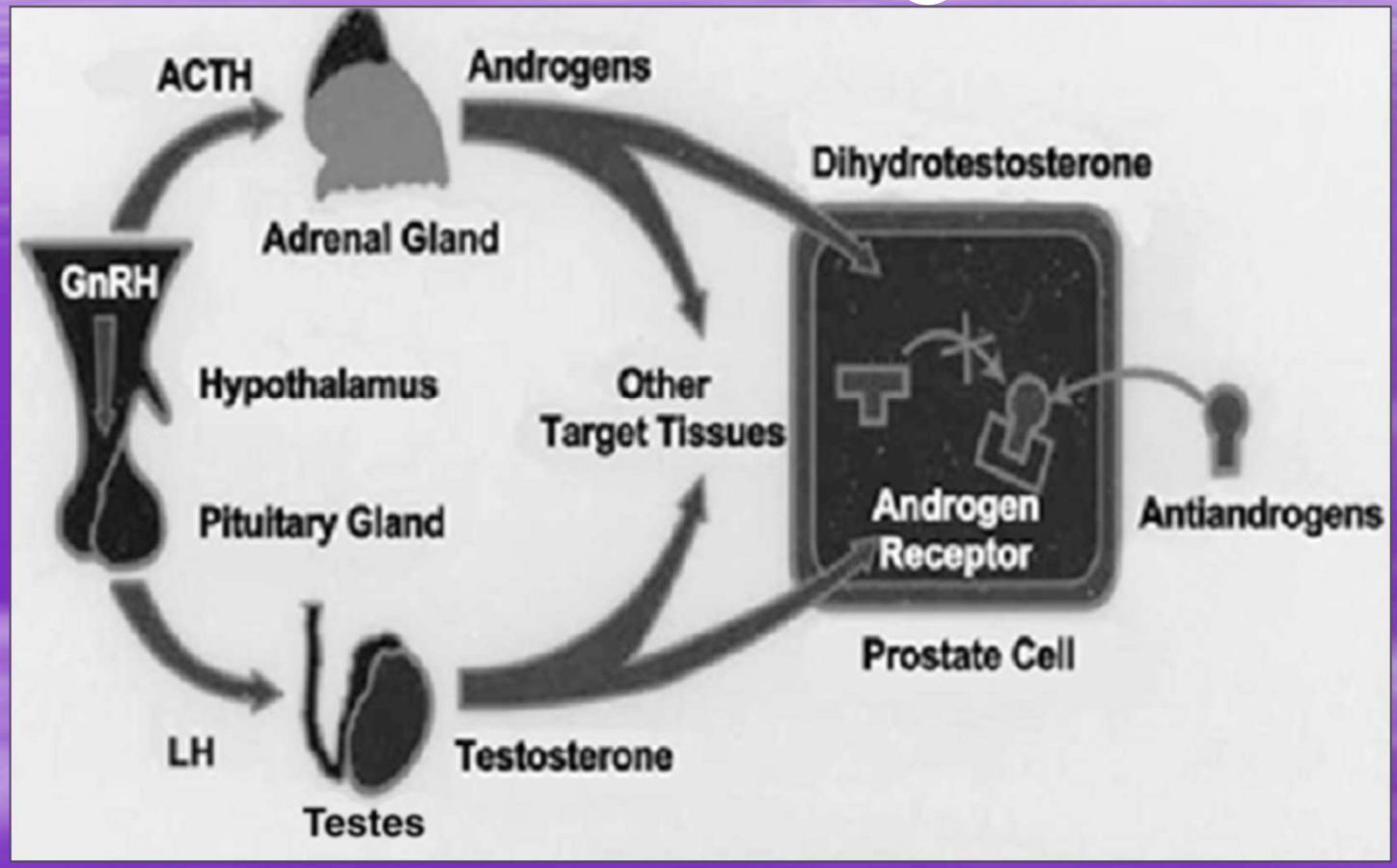
Kaisary et al 1991

Castration: Summary

- Patients prefer LHRH agonists vs surgical castration
  - LHRH agonist therapy can be reversed
- With 20 years' clinical experience, LHRH agonist therapy with goserelin has proven equivalent efficacy to surgical castration
- Goserelin is as effective as castration in terms of overall survival
- Compared with castration, goserelin offers[1]
  - higher QoL scores (p=0.0001)
  - improved psychosocial status (p=0.01)

1. Cassileth et al 1992

Mechanism of Action of Antiandrogens



GnRH = gonadotropin-releasing hormone

Goa KL, Spencer CM. *Drugs Aging.* 1998;12:401-422.

Rationale for Bicalutamide 150 mg monotherapy

- Bicalutamide 150 mg has shown equivalent efficacy to castration in M0 patients[1]
- Bicalutamide 150 mg may offer additional significant QoL advantages over castration

1. Iversen et al 2000

Bicalutamide150 mg in M0 disease

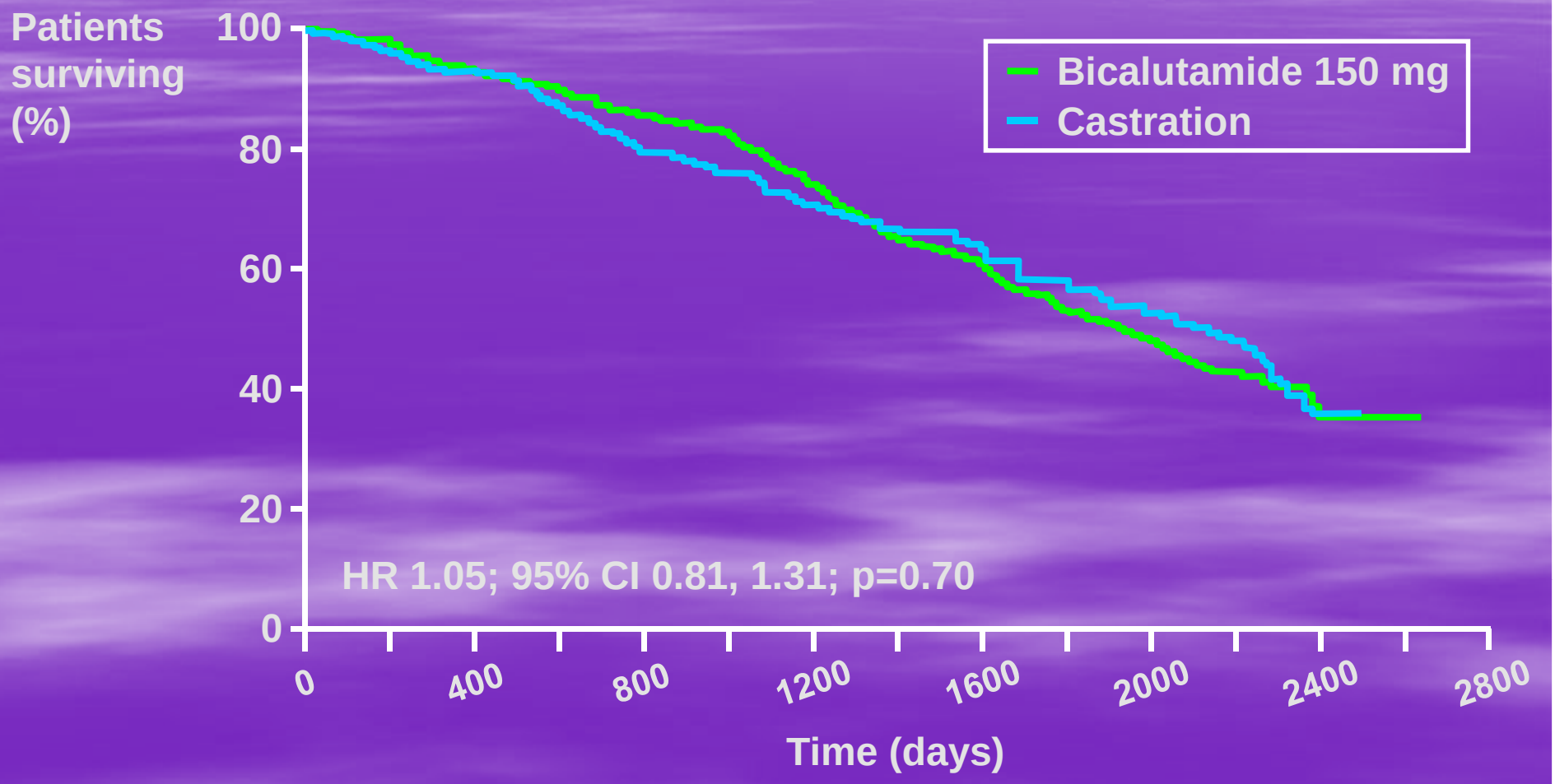
Studies 306 / 307

- Two open-label, multicentre studies that were pooled according to protocol
- 480 M0 patients with stage T3/4 prostate cancer were randomised 2:1 to receive
  - 150 mg bicalutamide daily

  OR
  - castration (patients chose either orchiectomy or goserelin 3.6 mg every 28 days)

Iversen et al 2000

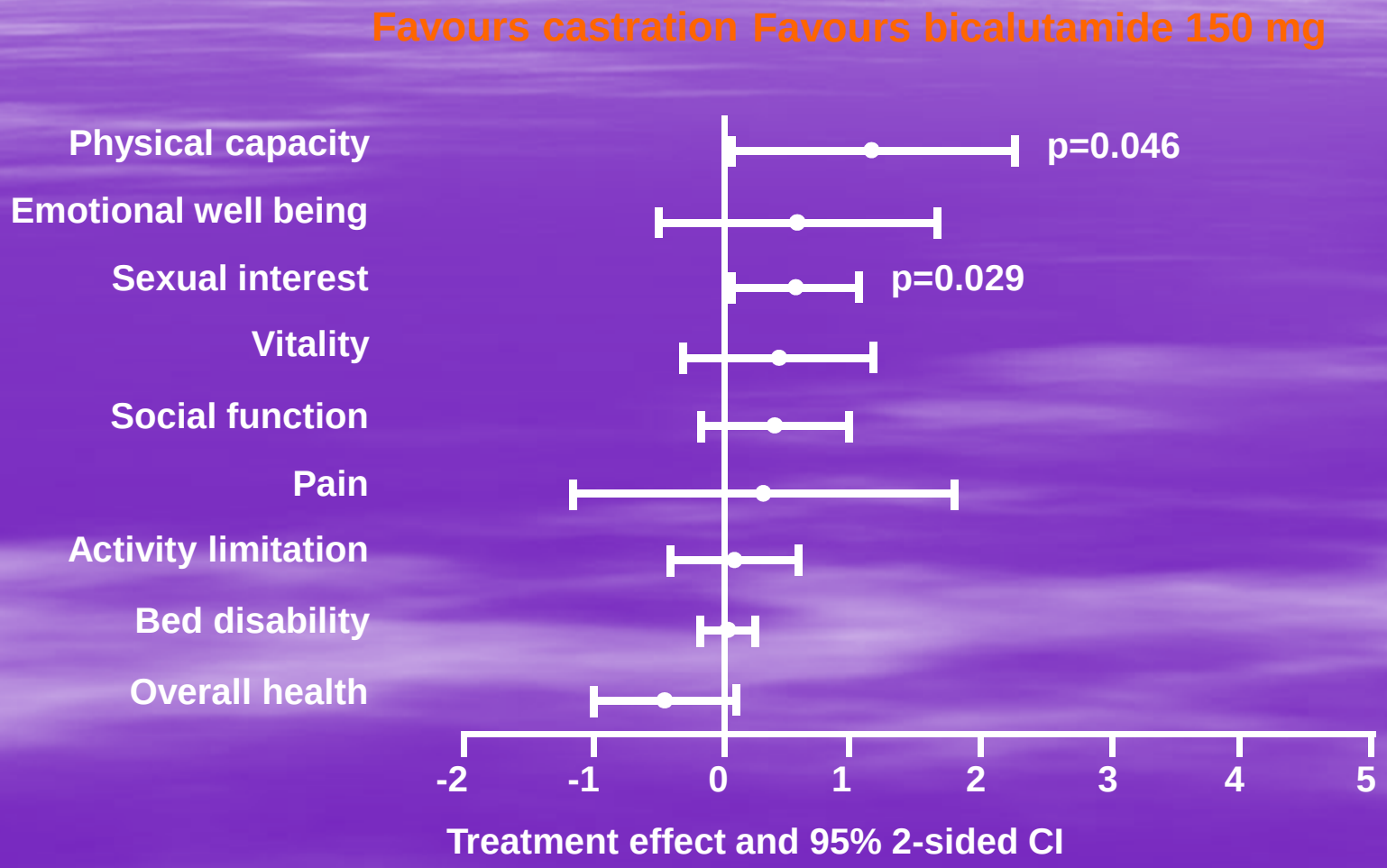
Overall survival in M0 patients:
Median 6.3 years' follow-up



Iversen et al 2000

CI, confidence interval; HR, hazard ratio

Bicalutamide 150 mg vs Castration Quality of Life: M0 Patients

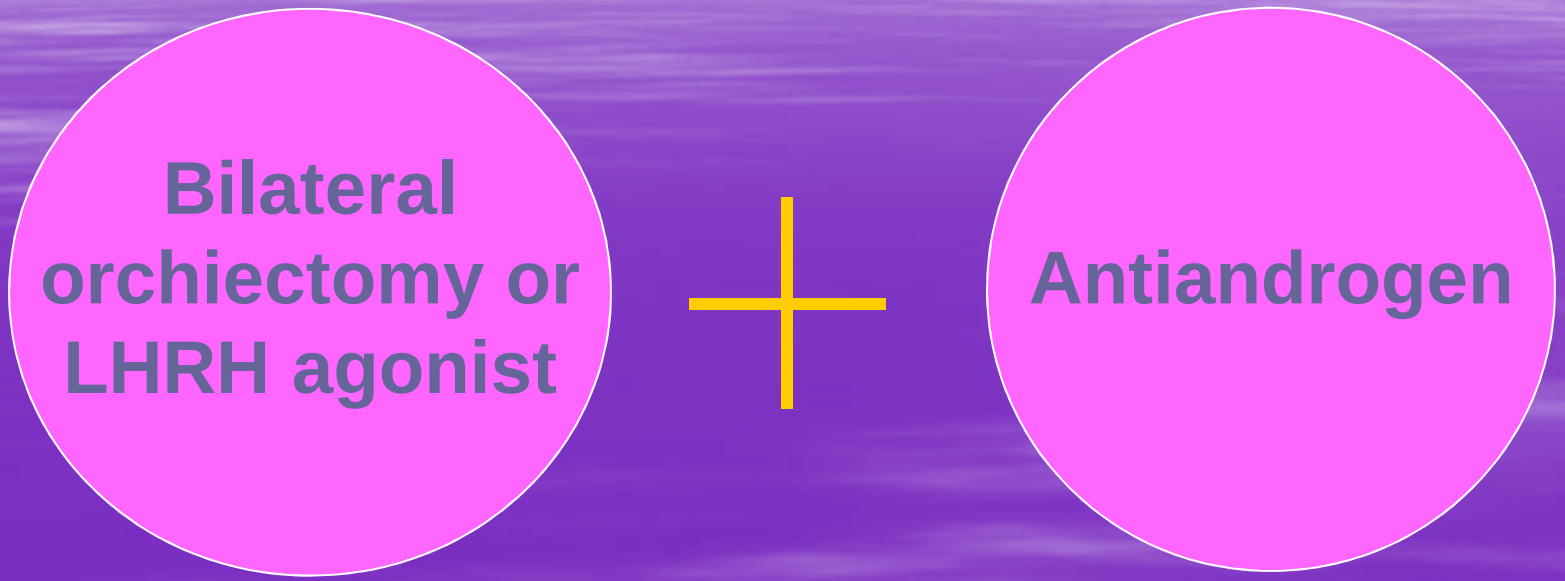


Iversen et al, Urology 1998

Anti-androgen Monotherapy: Summary

- Bicalutamide 150 mg is as effective as castration in patients with non-metastatic disease
- Bicalutamide 150 mg may offer QoL benefits over castration
- Bicalutamide 150 mg is a viable treatment option

Combined androgen blockade (CAB)



Suppression of serum testosterone

Blockade of androgen action

LHRH, luteinsing hormone-releasing hormone

The biological Rationale for CAB

- Addition of antiandrogen to castration further suppresses activity of androgens and the AR
- There is a strong biological rationale for CAB in the treatment of prostate cancer

Combination therapy PCTCG meta-analysis

- More recently, PCTCG meta-analysis of combination therapy versus monotherapy
  - 27 trials: 8275 men
  - 5-year overall survival favoured combination therapy (25.4% versus 23.6%)
  - overall 1.8% improvement in survival at 5 years

CAB: findings from the PCTCG meta-analysis (n=8275)

5-year survival favoured CAB (25.4% vs 23.6%)

Outcome dependent on choice of antiandrogen

With NON-STEROIDAL antiandrogens*, there was a significant 8% *reduction in the risk of death* (p=0.005)

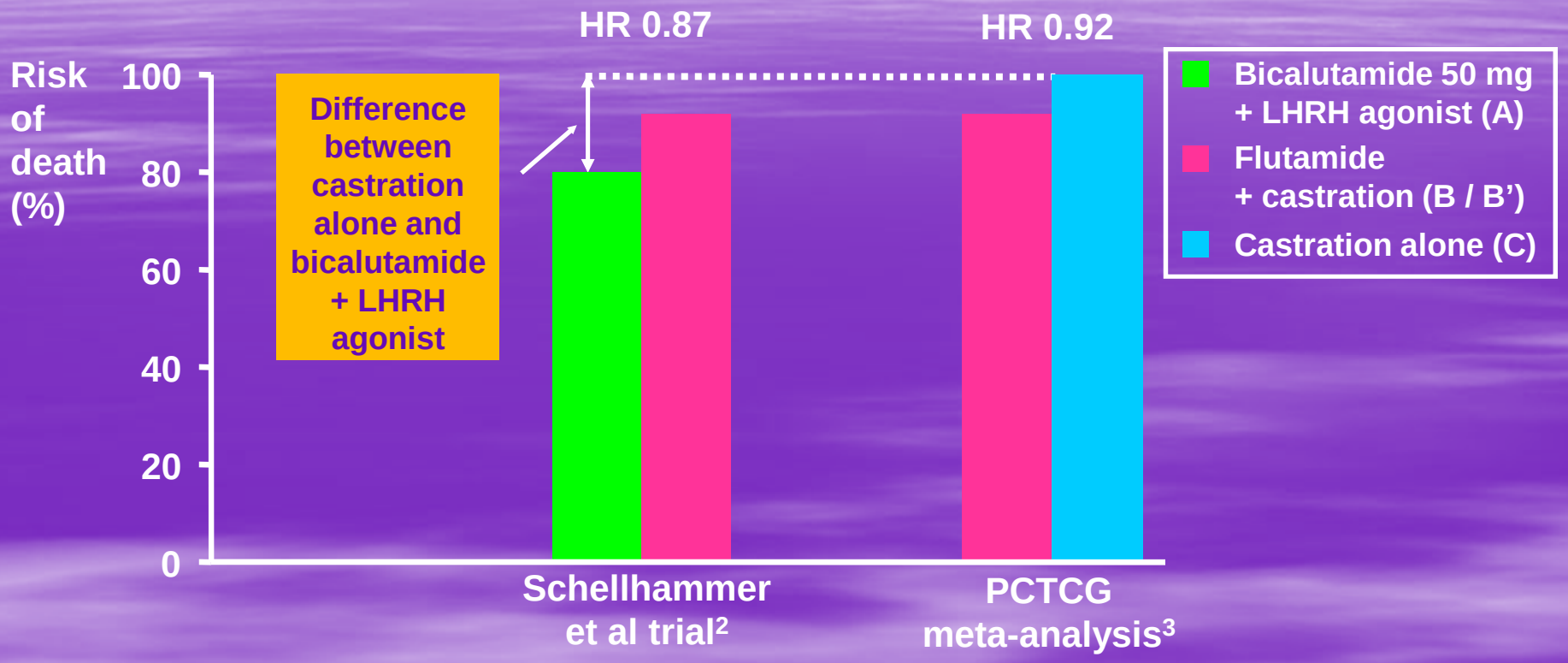
With STEROIDAL antiandrogens, there was a significant 13% *increase in the risk of death* (p=0.04)

*Flutamide or nilutamide

Klotz 2001; PCTCG 2000

PCTCG, Prostate Cancer Trialists' Collaborative Group

Adding Bicalutamide 50 mg to castration reduces the risk of death by 20%[1]

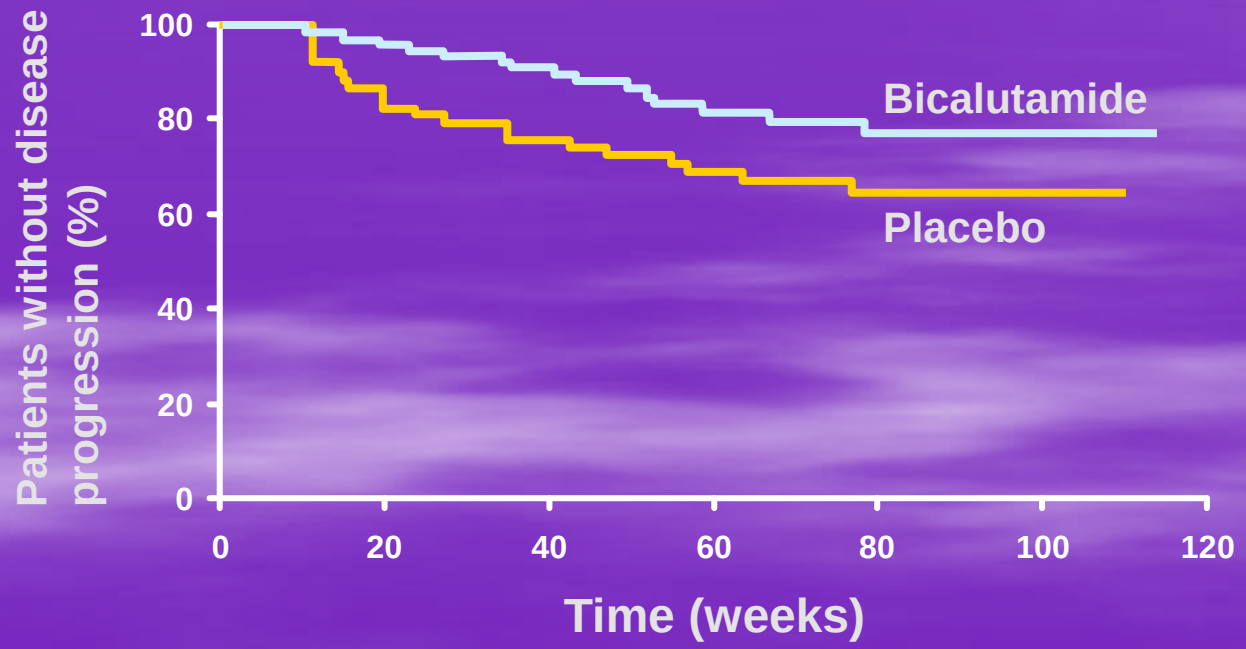


HR (A vs C)	=	HR (A vs B)	x	HR (B' vs C)
0.80	=	0. 87	x	0.92
20%	=	reduction in risk of death		

1. Klotz 2005; 2. Schellhammer et al 1997; 3. PCTCG 2000

CAB with Bicalutamide vs castration: phase III study

- LHRHa plus bicalutamide 80 mg vs LHRHa alone in advanced disease (n=205)
- At 15 months follow-up, PFS longer for CAB (p=0.016)

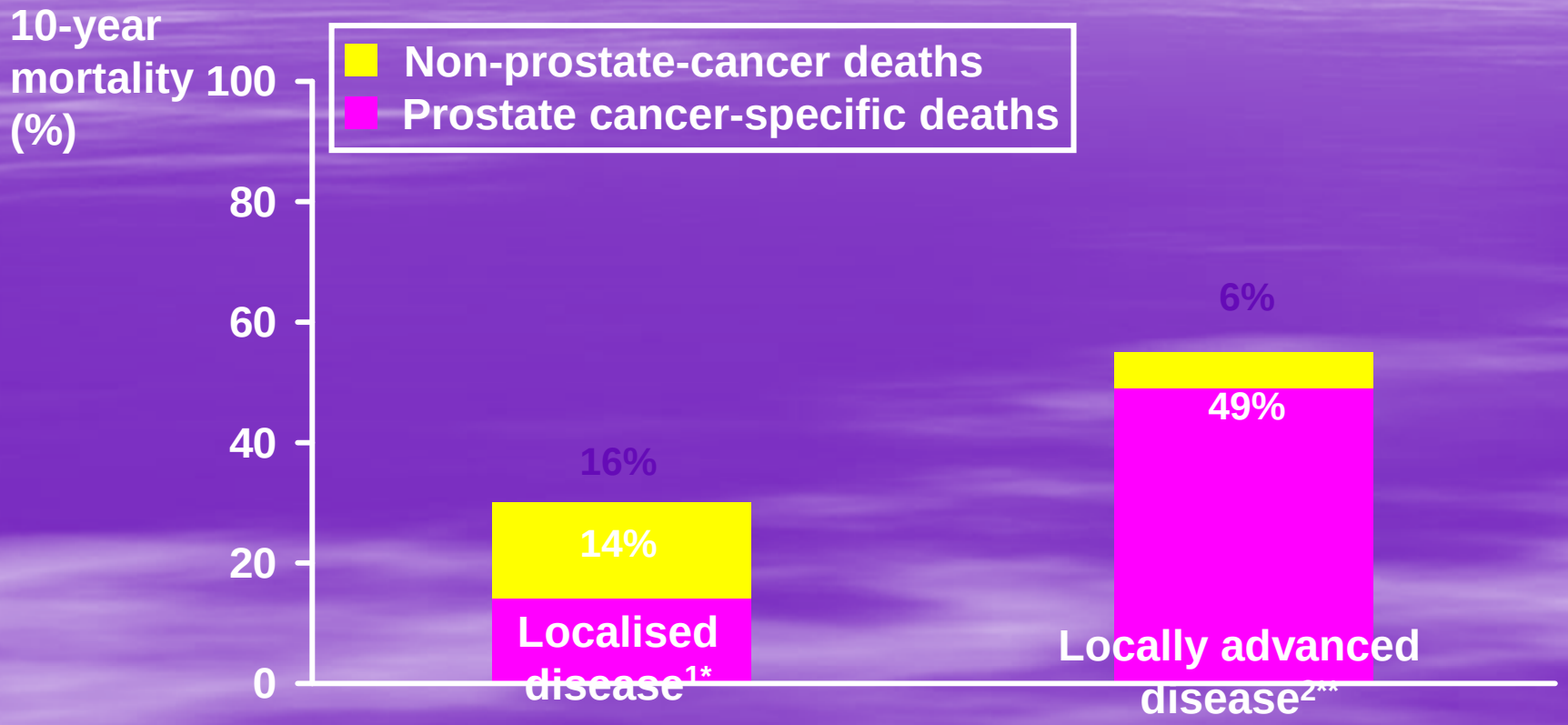


Akaza et al 2005

Is there a role for hormonal therapy in localised disease?

RP as primary treatment with adjuvant HT

Locally advanced patients have an increased risk of prostate cancer death after RP

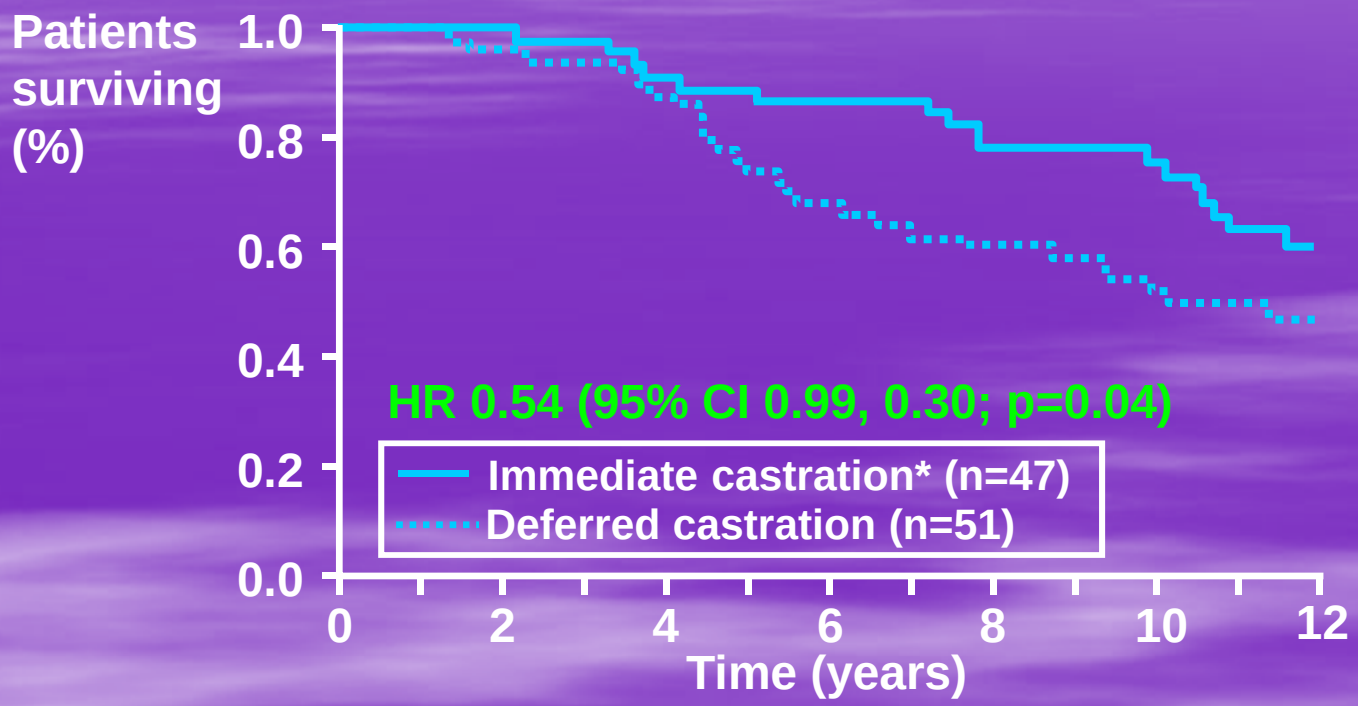


1. Bill-Axelson et al 2005; 2. Messing et al 2006

*Localised disease was defined as T1-2, M0 patients, >64% had GS <7

**Locally advanced disease was defined as pN+, M0 patients, >88% had GS >6

Immediate castration* adjuvant to RP significantly improves OS in N+ patients ECOG 7887 at 11.9 years' median follow-up

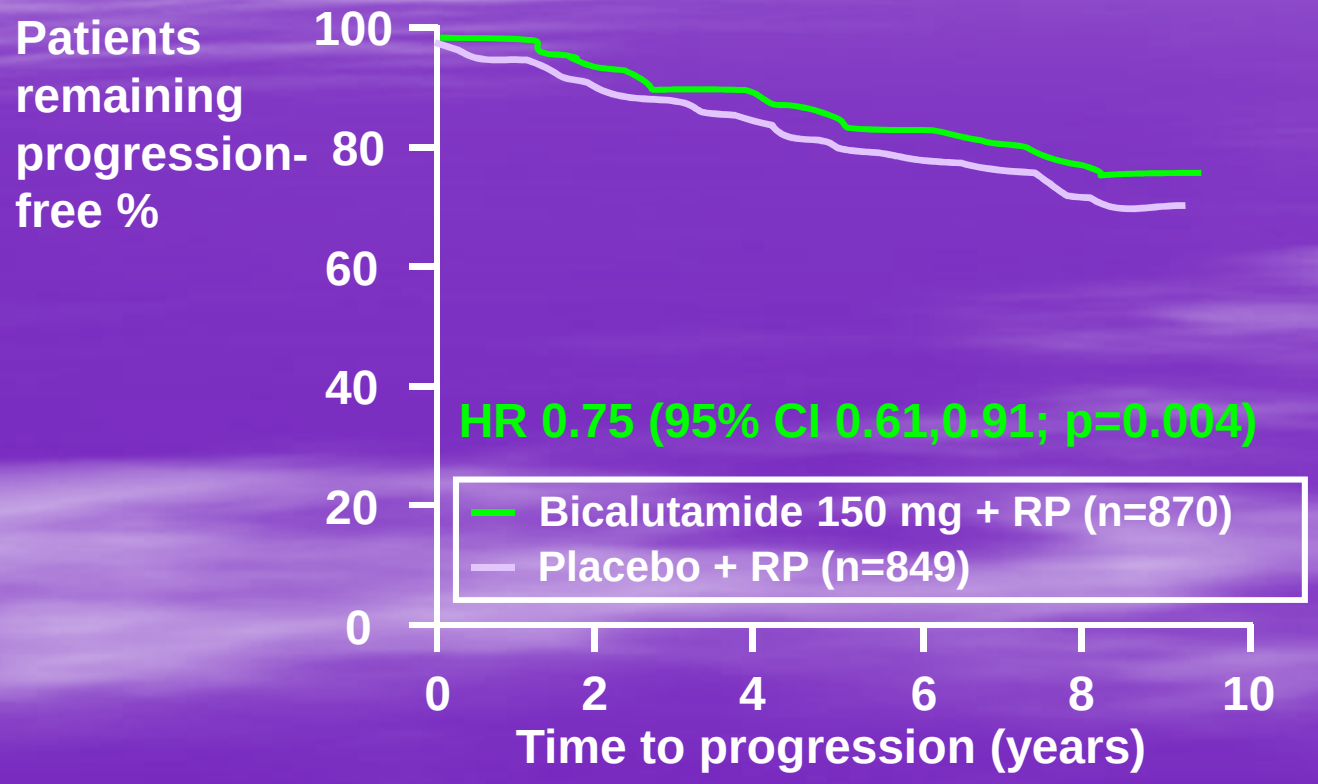


Goserelin adjuvant to RP significantly reduced the risk of death by 46% compared with RP alone

Messing et al 2006

*70% of patients received goserelin (Zoladex), 28% received orchiectomy and 2% refused treatment

Bicalutamide 150 mg adjuvant to RP provides progression benefits
EPC programme at 7.6 years' median follow-up



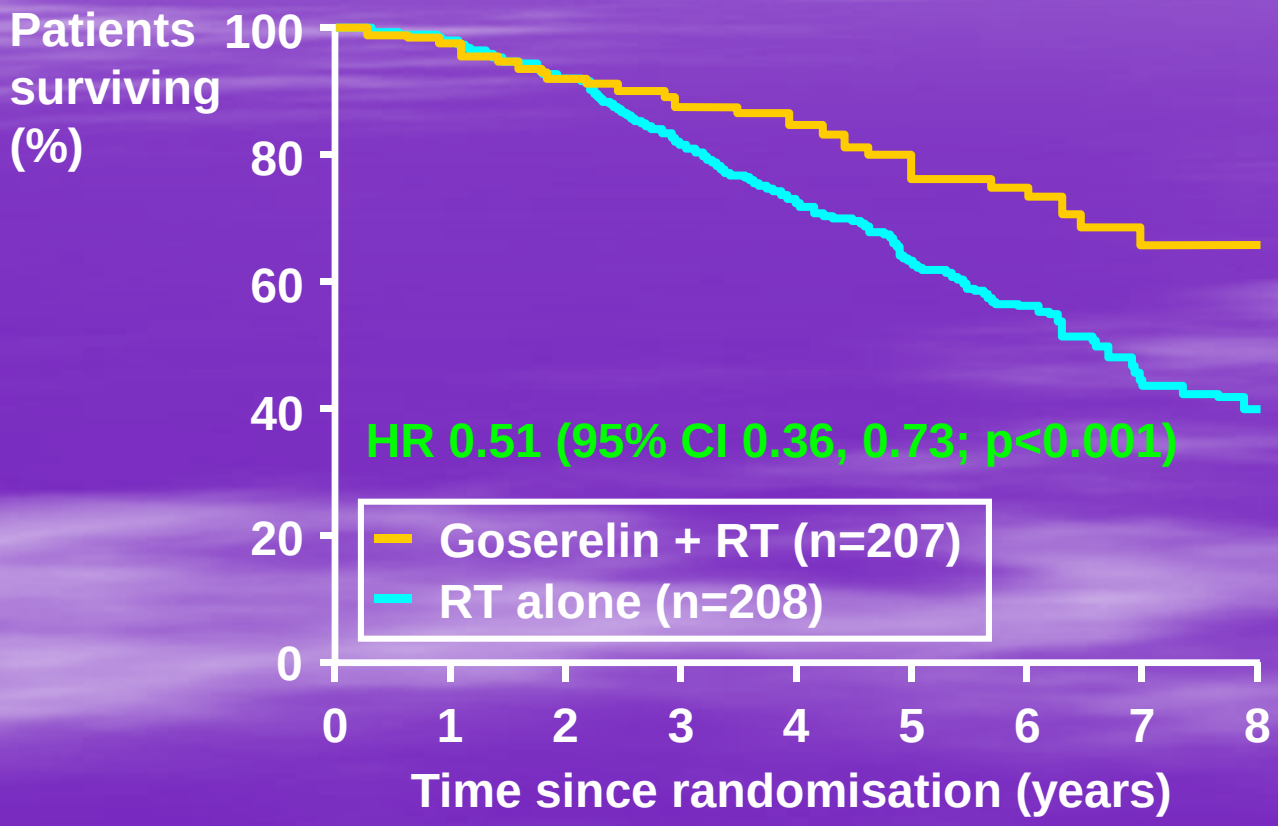
Bicalutamide adjuvant to RP significantly reduced the risk of progression by 25% compared with RP alone

There was no OS difference

McLeod et al 2006
T3-4 , any N, M0 or any T, N+, M0 patients

RT as primary treatment with adjuvant HT

Goserelin adjuvant to RT significantly improves OS EORTC 22863 at 5.5 years' median follow-up

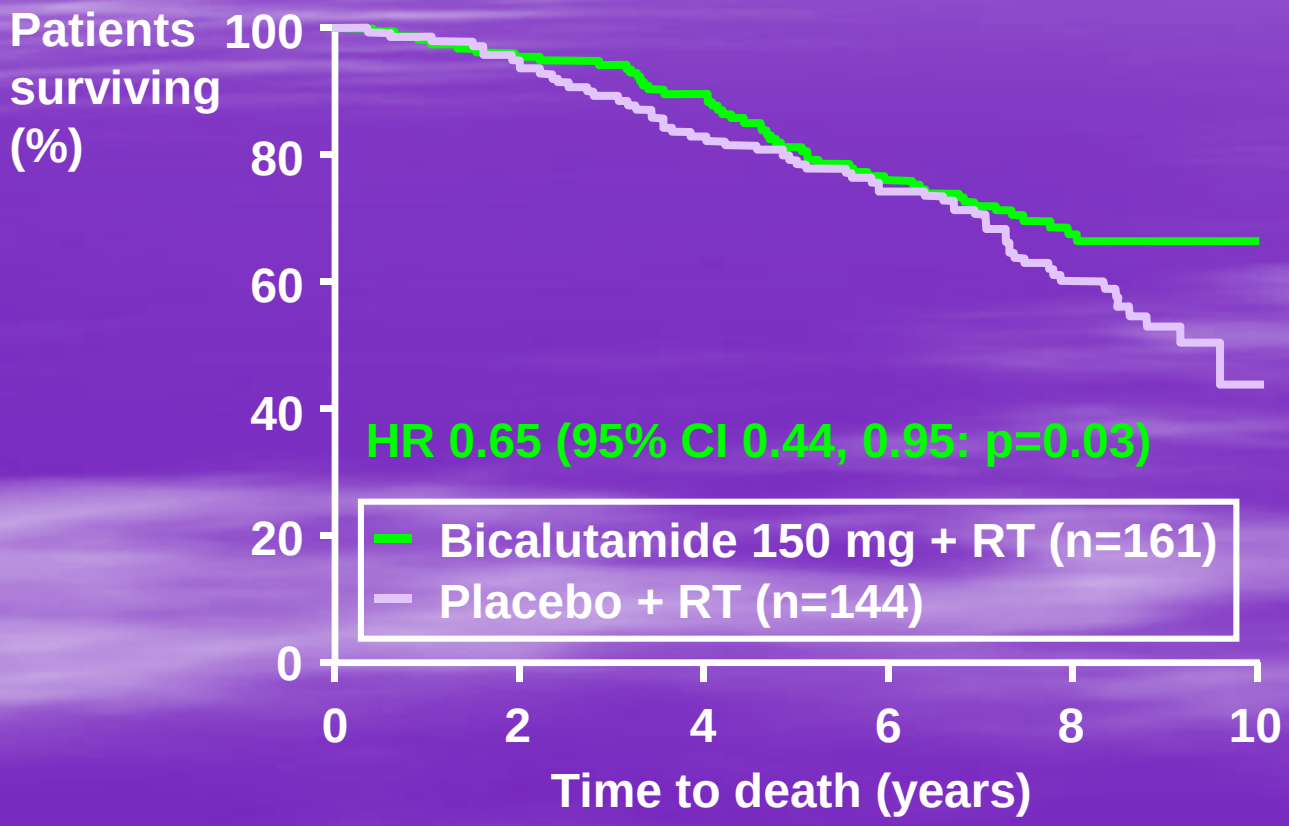


Goserelin adjuvant to RT significantly reduced the risk of death by 49% compared with RT alone

Bolla et al 2002

T1-2 of WHO grade 3 or T3-4 N0-1, M0 disease

Bicalutamide 150 mg adjuvant to RT significantly improves OS EPC programme at 7.2 years' median follow-up



Bicalutamide 150 mg adjuvant to RT significantly reduced the risk of death by 35% compared with RT alone

McLeod et al 2006
T3-4, any N; or any N, T, N+ patients

Summary: advantages of HT for patients with locally advanced disease

- HT adjuvant to RT and RP and as an alternative to WW offers clinical benefits[1]
- Bicalutamide 150 mg and goserelin have similar OS benefits as monotherapy and as adjuvant to RT[1-3]
- Bicalutamide 150 mg has additional quality-of-life benefits compared with castration; it maintains
  - sexual interest ($p=0.029$)[3]
  - physical capacity ($p=0.046$)[3]
  - BMD ($p<0.0001$ at 48, 72 and 96 weeks)[4]

The choice of therapy can be tailored to patients' individual needs

1. McLeod et al 2006; 2. Pilepich et al 2006; 3. Iversen 2000; 4. Sieber 2004

Intermittent hormonal therapy in advanced disease

- CAB is effective
- It has been suggested that intermittent therapy could potentially
  - prolong the response to hormonal therapy
  - improve QoL
- EAU 2005 guidelines[1] define intermittent therapy as ‘investigational’
- Phase III survival are now coming, data from ongoing studies are anticipated

1. Aus et al 2005

IAD: ongoing phase III studies

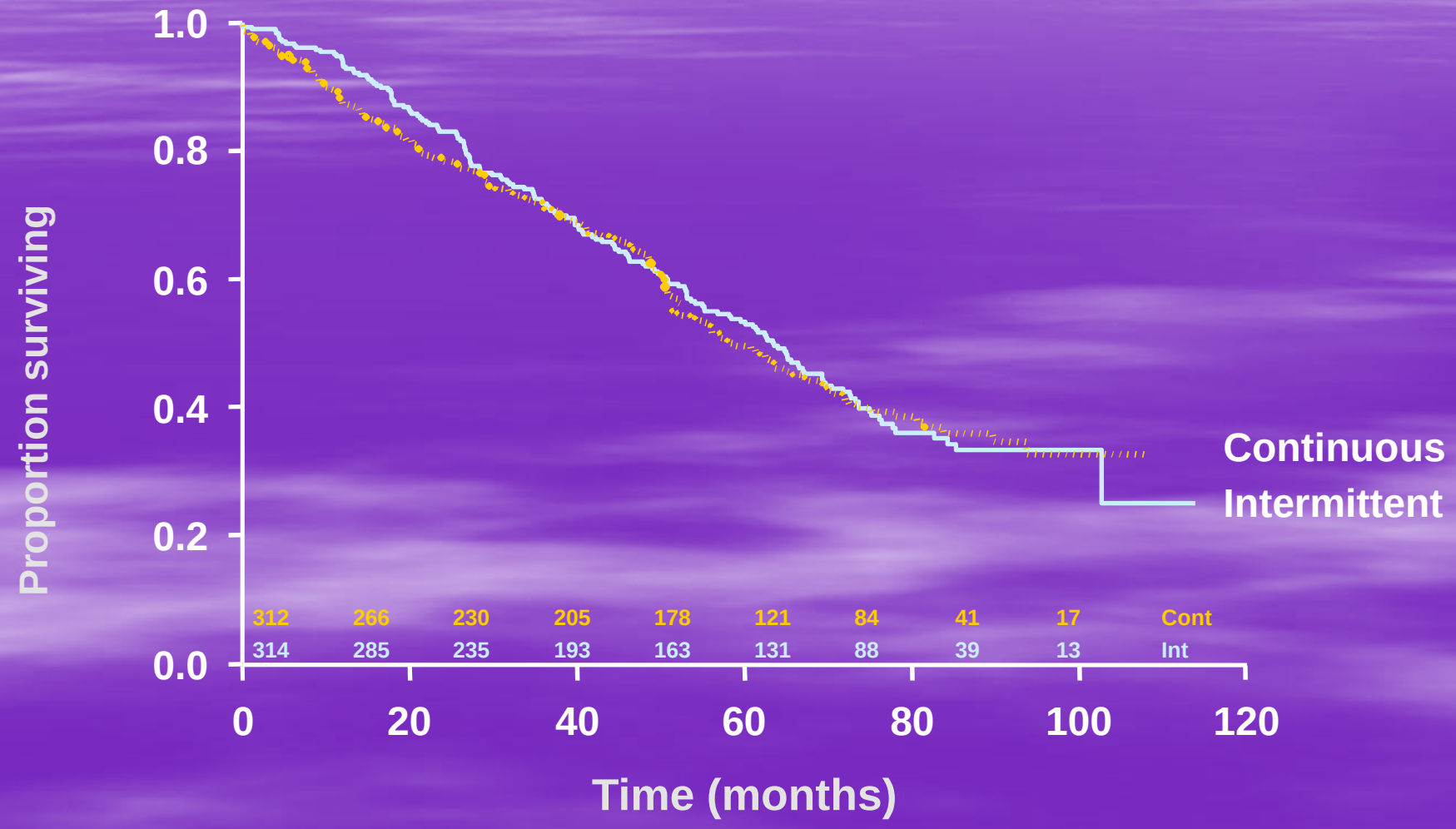
Portuguese trial

- 766 patients on HT, including CAB
- 626 randomised for continuous vs intermittent
  - 50% patients off therapy for ≥52 weeks
  - 20% patients off therapy for ≥36 months
- Responses linked to PSA at randomisation (<1 ng/mL)
- No difference in overall survival
  - HR for IAD 1.03 (95% CI, 0.83-1.28); p=0.79

Da Silva et al 2006

IAD: ongoing phase III studies

Portuguese trial: overall survival

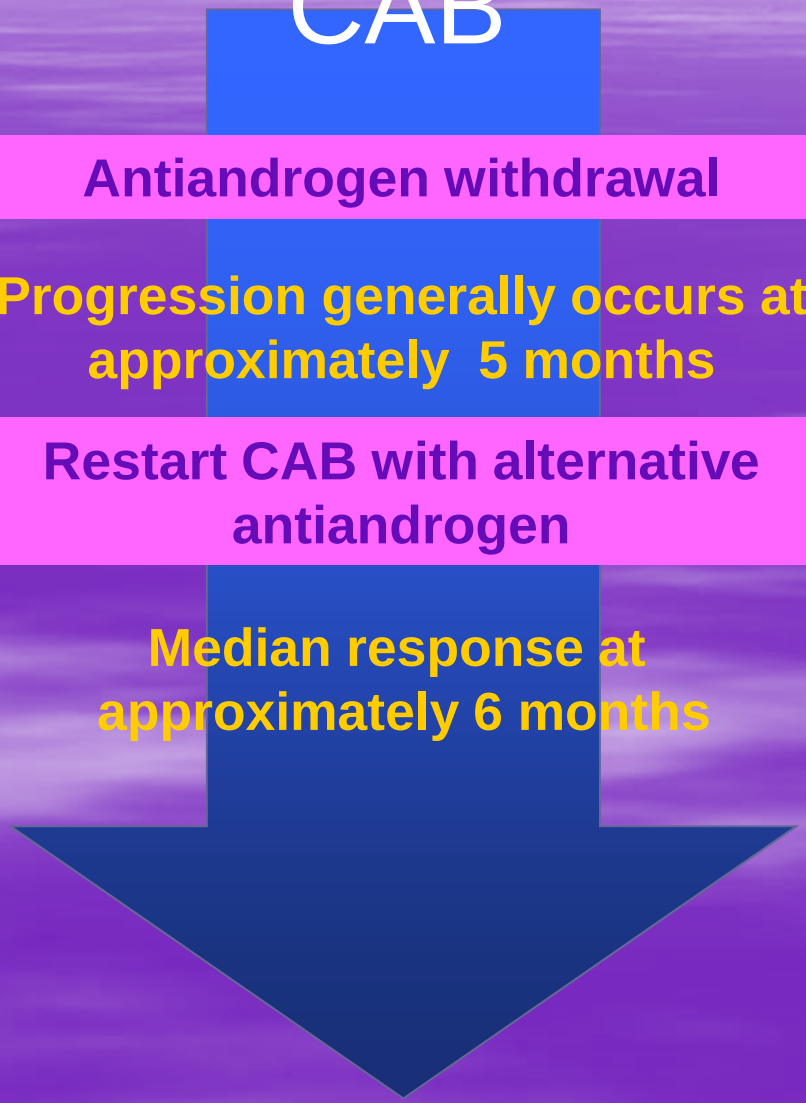


Da Silva et al, 2006

IAD: Summary

- Phase II trials have confirmed the feasibility of IAD in metastatic or biochemically recurrent disease
- PSA-response rates and improvements in symptoms are comparable to CAB
- Phase III prospective, randomised controlled trials are ongoing
  - survival and QoL data not yet mature
- IAD is currently offered to many patients in various clinical settings
- Until survival data mature, IAD should be regarded as an investigational approach

Antiandrogen withdrawal and second-line hormonal therapy in CAB



Antiandrogen withdrawal can reduce PSA levels: overview[1,2,3]

- Response criteria: ≥50% PSA decrease from baseline PSA level before antiandrogen withdrawal
- Response rate approx 25% (range 10-80%)
- Responses occurred within 2-6 weeks with flutamide and 4-8 weeks with bicalutamide
- Median response duration approx 5 months (range 2-25)
- Objective clinical response: 2-15% with antiandrogen withdrawal alone

1. Gleave 2004; 2. Small 2004; 3. Carroll 2003

Antiandrogen switching can prolong response to CAB: overview

- CAB with bicalutamide switched to flutamide:
  - 45% biochemical response rate
  - 22% durable response rate
  - Median response time 6 (1-13) months[1]
- CAB with flutamide switched to bicalutamide:
  - 38-42% of biochemical response rates[2,3]
- CAB with flutamide switched to bicalutamide or bicalutamide switched to flutamide:[4]
  - second-line flutamide response rate = 38%
  - second-line bicalutamide response rate = 44%
  - switching to a third-line antiandrogen was less effective

1. Miyake 2004; 2. Scher 1997; 3. Joyce 1998; 4. Kojima 2004

PROSTATE CANCER

Overview of Hormone responsive Prostate Cancer

- Neo adjuvant AAT is shown to prolong survival in high risk patients treated with RT & RP
- Earlier AAT is better than delayed AAT as it delays appearance of symptoms and metastases in recurrent disease.
- LHRH agonists and bilateral orchiectomy is equally effective
- MAB limited benefit over castration

PROSTATE CANCER

Overview of Hormone responsive Prostate Cancer

- Anti androgens should precede LHRH agonists in patient with overt metastases.
- Anti androgen monotherapy is less effective than castration.
- Intermittent androgen ablation to reduce side effects – long efficacy remains unproven.
- Androgen receptors active in HRPC. Thus testosterone suppression to continue.

THANK YOU