Καρκίνος του προστάτη: η τελευταία πράξη

Δ. Μητρόπουλος
Α. Σκολαρίκος

Περίπτωση 1

Ανδρας 68 ετών με LUTS (συχνουρία, επιτακτικότητα, δυσουρία) και πρόσφατα επεισόδια αιματουρίας και ακράτειας. Επιπλέον των ουρολογικών συμπτωμάτων αιτιάται ήπιο σταθερό πόνο στην οσφύ και περιστασιακή δυσκοιλιότητα.
ΔΕΠ: Διογκωμένος προστάτης με πολλαπλά ψηλαφητά σκληρά οζίδια.
PSA: 95 ng/mL (6 χρόνια πριν: 1,5 ng/mL). Λοιπά: κ.φ.
TRUS: Πολλαπλές υποηχογενείς και υπερηχογενείς εστίες
Βιοψία προστάτου: Καρκίνος προστάτη Gleason score 4+4=8
Αξονική τομογραφία θώρακος και κοιλίας: χωρίς μεταστάσεις σε λεμφαδένες/συμπαγή όργανα
Ολόσωμο σπινθηρογράφημα οστών: πολλαπλές εστίες καθήλωσης του ραδιοφαρμάκου στη σπονδυλική στήλη
MRI σπονδυλικής στήλης: μεταστατική εστία στον Θ10 με κατάληψη όλου του σπονδύλου, χωρίς πίεση του μυελού

Στάδιο της νόσου: T3βN0M1β.

Περίπτωση 2

Ανδρας 66 ετών, ασυμπτωματικός, ανευρίσκει σε έλεγχο ρουτίνας PSA 22 ng/ml.
Ιατρικό ιστορικό: προ 3ετίας έμφραγμα μυοκαρδίου και 3πλό by-pass
ΔΕΠ: Ελαφρά διογκωμένος προστάτης, διάχυτα υπόσκληρος, ομαλός.
Βιοψία προστάτου: Καρκίνος προστάτη Gleason score 4+4=8 άμφω
Αξονική τομογραφία θώρακος και κοιλίας: χωρίς μεταστάσεις σε λεμφαδένες/συμπαγή όργανα
Ολόσωμο σπινθηρογράφημα οστών: 2 εστίες καθήλωσης του ραδιοφαρμάκου στις πλευρές και 1 στο λαγόνιο.

Στάδιο της νόσου: T2βN0M1β.

Ερωτήματα:

1)Υπάρχει διαφορά στην αντιμετώπιση των δύο ασθενών;
2)Αμεση ή καθυστερημένη έναρξη;
3)Διακοπτόμενη ή συνεχής θεραπεία;
4)Εχει θέση η χημειοθεραπεία;
5)Χρειάζεται υποστηρικτική θεραπεία ο σκελετός και αν ΝΑΙ, ποιά;

Ερωτήματα:

1)Υπάρχει διαφορά στην αντιμετώπιση των δύο ασθενών;

M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up.	B
	Radical prostatectomy	Not a standard option.	C
	Radiotherapy	Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms.	C
	Hormonal	Standard option. Mandatory in symptomatic patients.	A

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Table 18: Indications for hormonal therapy

Hormonal therapy Indications for castration	Benefits	LE
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).	1b
	Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence.	1
M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b
	An active clinical surveillance protocol may be an acceptable option in clearly informed patients if survival is the main objective.	3
N+	Immediate castration to prolong PFS and even OS.	1b
	Might be questioned in single micrometastasis after extended lymph node dissection and radical prostatectomy.	3

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Table 19: Contraindications for various therapies.

Therapy	Contraindications
Bilateral orchiectomy	Psychological reluctance to undergo surgical castration.
Oestrogens	Known cardiovascular disease.
LHRH agonists alone	Patients with metastatic disease at high risk for clinical 'flare up' phenomenon.
Anti-androgens	Localised PCa as primary therapy.

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ADVERSE EFFECTS OF ADT

System	Side Effect	Strategies to Alleviate/Manage
Sexual	Impotence	Erectile dysfunction therapy
	Loss of libido	Counseling
Metabolic	Dyslipidemia	Diet, exercise
	Diabetes mellitus	Statins
Body habitus	Obesity	Diet, exercise, nutrition consult
	Gynecomastia, breast tenderness	Statins
	Hair loss	Calcium, vitamin D
	Loss of muscle mass	Bone mineral density surveillance, exercise against gravity, bisphosphonates
	Loss of bone mass	
Systemic	Hot flashes	Intermittent androgen deprivation
	Night sweats	Erythropoietin
	Fatigue	
	Anemia	
Cognitive/Psychosocial	Depression	Antidepressants
	Lack of initiative	Counseling
	Emotional lability	

ANTIANDROGENS

Antiandrogen	Dose	Side-Effects
As a class		Nausea, vomiting, diarrhea, breast enlargement, breast tenderness, hepatotoxicity
Flutamide	250 mg tid	Hepatotoxicity (in particular)
Nilutamide	300 mg/d for 30 d and then 150 mg/d	Decreased dark adaptation, interstitial pneumonitis (rare), alcohol intolerance
Bicalutamide	50 mg/d	Breast enlargement, breast tenderness (in particular)

Ερωτήματα:

2) Άμεση ή καθυστερημένη έναρξη;

Πρέπει η ADT να ξεκινά άμεσα με τη διάγνωση της τοπικά προχωρημένης και ασυμπτωματικής μεταστατικής νόσου;

Μεταστατική Νόσος

Πρώιμη ή Καθυστερημένη ορμονική θεραπεία;

- **VACURG**: κανένα πλεονέκτημα *OS*
- **MRC** : καθυστέρηση εμφάνισης μεταστάσεων, μείωση οστικών επιπλοκών (≥T3, ασυμπτωματική μεταστατική νόσος)
- **Cochrane:** Αυξάνει 10y *OS, CSS, PFS* (*VACURG -1 , VACURG-II, MRC, ECOG* σε ασθενείς με ιστολογική λεμφαδενική συμμετοχή μετά RP)

Επιλογή χρόνου ορμονοθεραπείας σε N+ νόσο

- Ανασκοπικά στοιχεία από την Mayo Clinic, υποδηλώνουν όφελος για την πρώιμη ορμονοθεραπεία (ΕΗΤ)[1]
  - Το όφελος μόνο σε διπλοειδείς όγκους[1]
- Προπτικά στοιχεία από EORTC 30846 υποδηλώνουν όφελος για την πρώιμη ορμονοθεραπεία (ΕΗΤ)
  - Χρόνος έως την μετάσταση 1.8, έναντι 5 έτη[2]
  - Συνολική επιβίωση: **HR 1.22** (0.92-1.62)[3]
- Η ECOG 7887, υποδηλώνει όφελος για την πρώιμη ορμονοθεραπεία[4]

[1] Zincke et al., J Urol. 1992
[2] Van den Qunden et al., Eur Urology 1993
[3] Schroeder et al., Eur Urology 2009
[4] Messing et al AUA 2003

Επιλογή χρόνου ορμονοθεραπείας σε M+ νόσο

- Αρχικά η μελέτη MRC έδειξε καλύτερη επιβίωση για την πρώιμη ορμονοθεραπεία
  - Ουδεμία διαφορά για νόσο M+ [1]
  - Ουδεμία διαφορά στη επιβίωση 3 έτη αργότερα [2]
  - Λιγότερες όμως επιπλοκές με την πρώιμη ορμονοθεραπεία [2]
    - **Συμπίεση Ν.Μ. 1.9 vs 4.9%**
    - **Απόφραξη του ουρητήρα 7.0 vs 11.8%**
    - **TURP 13.9 vs 30.3%**
- Ουδεμία διαφορά στη συνολική επιβίωση(SAKK 08/88)[3]
- Σημαντική διαφορά στη συνολική επιβίωση στα 10 έτη [4]
  - 67.9% vs 61% @ 5 έτη
  - **36.1% vs 25% @ 10 έτη**

[1]MRC, BJU 1997;79:235-246
[2]Kekk et al,BJU Int 2000;86(s 3):220
[3] Studer et al J Clin. Oncol 2004; 22: 4109-4118
[4] Studer et al , Eur. Urol., 2005;3(S4): 78

- ADT is the treatment of choice for patients with metastatic disease, although the literature analyzing deferred treatment of asymptomatic M+patients is sparse. Because median survival in metastatic patients at diagnosis is now approximately 5–6 yr and further cancer progression can cause severe adverse effects, the EAU guidelines suggest that ADT should only be delayed in patients who strongly wish to avoid treatment-related side effects. In symptomatic M+ PCa patients, ADT should be given immediately to palliate symptoms

European urology 55 (2 0 0 9) 62–75

Ερωτήματα:

3) Διακοπτόμενη ή συνεχής θεραπεία;

Η λογική της διακεκομμένης καταστολής των ανδρογόνων (IAS)

- Ένα χαρακτηριστικό του διαφοροποιημένου προστατικού κυττάρου είναι η ικανότητα να υφίσταται απόπτωση
- Η στέρηση των ανδρογόνων μετατρέπει τα κύτταρα σε αδιαφοροποίητα
- Η επανέκθεση σε ανδρογόνα δίνει τη δυνατότητα στα κύτταρα να επαναδιαφοροποιηθούν
- Αναμένεται καθυστέρηση στην ευνουχο-αντοχή;;
- Καλύτερη QoL

SWOG - 9346

PSA value as cut-off point	Median survival (mo)
< 0,2ng/ml	75
< 4ng/ml	44
> 4ng/ml	13

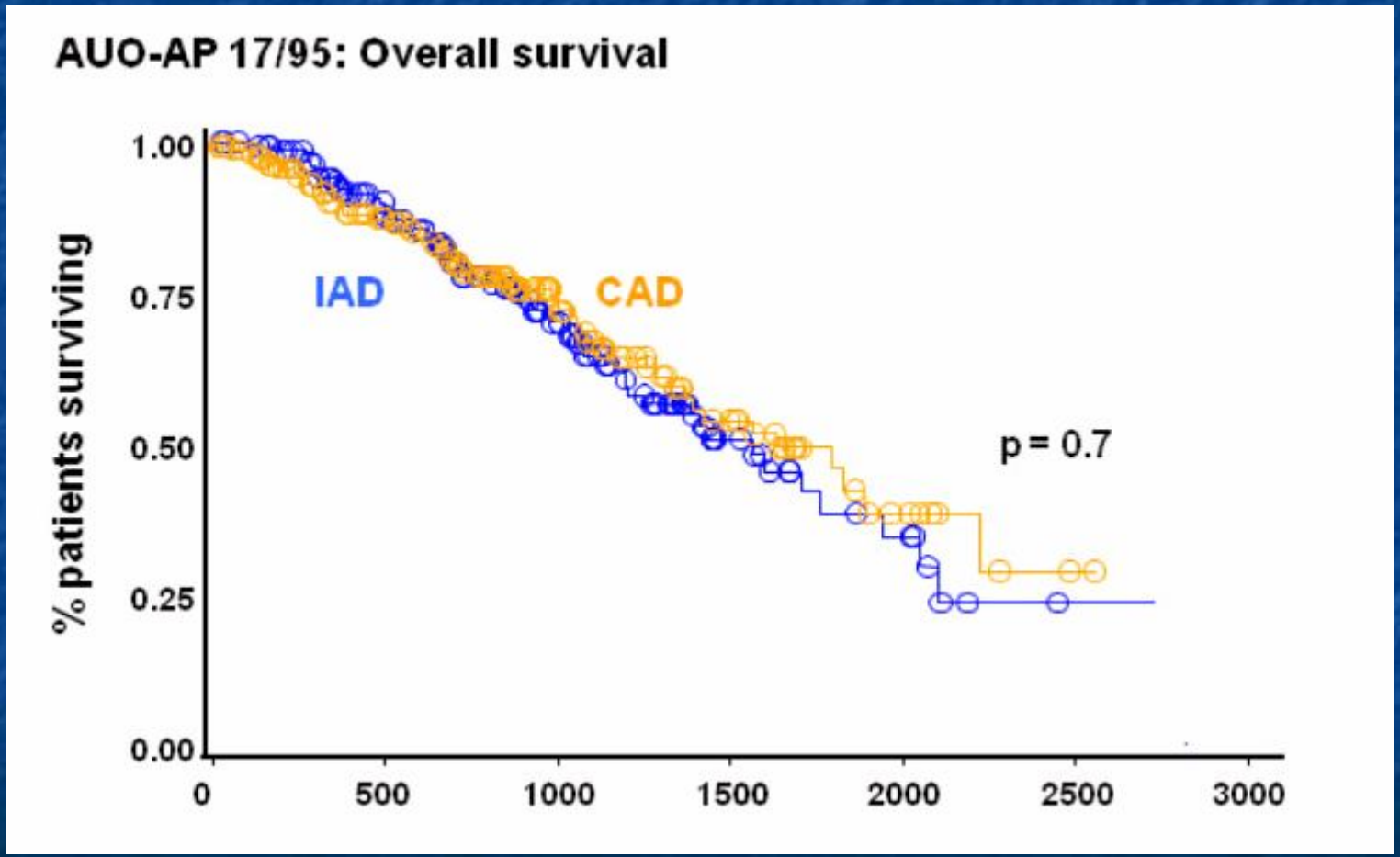
Hussain M, Tangen CM, Higano C, et al. ,J Clin Oncol 2006;24:3984-90.

Η λογική της διακεκομμένης καταστολής των ανδρογόνων (IAS)

TRIAL	N	SETTING	TREATMENT	RESULTS
deLeval *et al.* Clin Prostate Cancer 2002[6]	68	advanced (T3-4, N+, M+, relapsed after RP)	goserelin acetate + flutamide	lower androgen-independent progression rate for intermittent arm
Miller *et al.* ASCO 2007 (abstract #5015) [8]	335	N+, M+	goserelin acetate + bicalutamide	similar time to disease progression and survival, improved QoL
Calais de Silva *et al.* ASCO 2006 (abstract #4513)[9]	626	T3-4, N+, M+	triptorelin pamoate + cyproterone acetate	similar time to disease progression and survival, improved QoL

ASCO, American Society of Clinical Oncology; AUA, American Urological Association; T3-4, locally advanced disease; N+, metastases in locoregional nodes, M+, distant metastases; PSA, prostate-specific antigen; RP, radical prostatectomy; QoL, quality of life

Διακεκομμένη καταστολή των ανδρογόνων



Courtesy of Prof. K. Miller, 2008

Μελέτη φάσης III συγκρίνοντας ΔΑΑ με ΣΑΑ σε ασθενείς με BY *PSA* μετά ριζική τοπική θεραπεία

- Συνολική επιβίωση ίδια και στα δύο σκέλη
- Αλλά.....
  - Ασθενείς σε ΔΑΑ είναι περισσότερο πιθανό να πεθάνουν από *Ca* - προστάτη **17.3% vs 14%** (+ 26% αύξηση)
  - Ασθενείς σε ΣΑΑ είναι περισσότερο πιθανό να πεθάνουν από άλλα αίτια **60% vs 52.3%** (+ 14% αύξηση)
- Πολλοί ασθενείς επιλέγουν τον τρόπο που θέλουν να πεθάνουν

Klotz et al, JCO 2011; S7:abstr 3

Διακεκομμένη καταστολή των ανδρογόνων - ΑΕ

Κατηγορία των ανεπιθύμητων συμβάντων	ΔΑΑ%	ΣΑΑ%
Οιοδήποτε ανεπιθύμητων συμβάντων	53.9%	47.6%
Σοβαρά ανεπιθύμητα συμβάντα (ΣΑΣ)	32.7%	30.6%
ΣΑΣ που οδηγούν στον θάνατο	9.09%	7.06%
Διακοπή της μελέτης οφειλόμενη στα ΑΣ	8.48%	7.65%
Επίσχεση ούρων	5.45%	1.18%
Καρδιακή ανεπάρκεια	1.82%	0.0%
Έμφραγμα μυοκαρδίου	3.03%	2.35%

Courtesy of Prof. K. Miller, 2008

Συμπερασματικά

- Τα στοιχεία από τις κλινικές μελέτες είναι πτωχά
  - Μόνο δύο ώριμες μελέτες φάσης ΙΙΙ μέχρι τώρα
  - Η ποιότητα ζωής ποτέ δεν έχει ερευνηθεί σωστά
  - Σύγκριση με το ΣΑΑ: ουδεμία διαφορά στην PFS , και OS
- Παραμένουν περισσότερες ερωτήσεις από απαντήσεις
  - Ποιοί ασθενείς (M1, cT3, βιοχημική υποτροπή PSA , κλπ)
  - Πότε διακόπτεται;; πότε επαναλαμβάνεται η θεραπεία;;
  - Ποιό είδος θεραπείας (MAB;;)

In conclusion, IAD is currently widely offered to patients with PCa in various clinical settings, and its status should no longer be regarded as investigational (LE: 2).

- The initial (induction) cycle must last between 6 and 9 months, otherwise testosterone recovery is unlikely.
- The treatment is stopped only if patients have fulfilled all the following criteria:
  - well-informed and compliant patient
  - no clinical progression, i.e. a clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease, or 0.5 ng/mL in relapsing disease.
- Strict follow-up must be applied once treatment has stopped, with clinical examination every 3-6 months. The more advanced the disease, the closer is the follow-up). The PSA level should be measured by the same laboratory to ensure standardization of testing.
- Treatment is resumed when the patient reaches either a clinical progression, or a PSA value above a predetermined, empirically fixed threshold. This is usually 4-10 ng/mL in non-metastatic situations or 10-15 ng/mL in metastatic patients (80).
- The same treatment is used for at least 3-6 months.
- Subsequent cycles of treatment are based on the same rules until the first sign is seen of hormone-refractory status.

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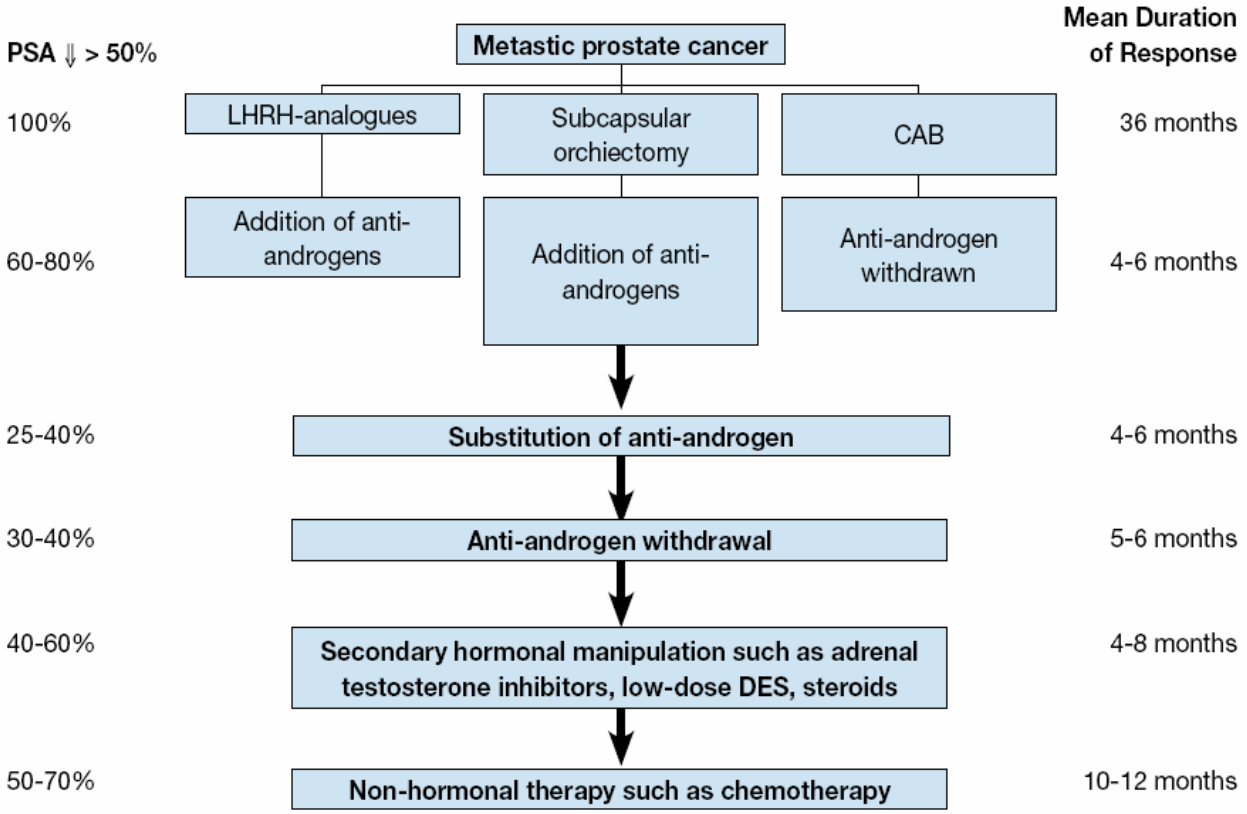
Ερωτήματα:

4)Έχει θέση η χημειοθεραπεία;

Figure 1: Flowsheet of the potential therapeutic options after PSA progression following initial hormonal therapy



LHRH = luteinising hormone releasing hormone; CAB = complete androgen blockade; DES = diethylstilboesterol.

Μόνο σε CRPC

Table 24: PSA response rates, mean survival, time to progression, and pain reduction in the large, prospective, randomised phase III trials of chemotherapy in patients with CRPC

Study	n	PSA decrease > 50%	Decrease in pain	Survival (months)	Time to progression
TAX 327					
Mitoxantrone, 3 weekly, 12 mg/m^2, Prednisone 5 mg BID		32%	22%	16.5	-
Docetaxel, 3 weekly, 75 mg/m^2 Prednisone 5 mg BID		45%[1]	35%[3]	18.9[1]	-
Docetaxel, weekly, 30 mg/m^2 Prednisone 5 mg BID		48%[1]	31%	17.4	-
SWOG 99-16					
Mitoxantrone, 3 weekly, 12 mg/m^2	336	50%[1]	-	17.5[2]	6.3 months[1]
Docetaxel/EMP, 3 weekly, 60 mg/m^2, EMP 3x280mg/day	338	27%	-	15.6	3.2 months
CALGB 9182					
Hydrocortisone	123	38%[4]	-	12.3	2.3 months
Mitoxantrone/HC, 3 weekly, 12 mg/m^2	119	22%	-	12.6	3.7 months[4]
Tannock et al.					
Prednisone	81	22%	12%	-	43 weeks[1]
Mitoxantrone/Pred, 3 weekly, 12 mg/m2	80	33%	29%[2]	-	18 weeks

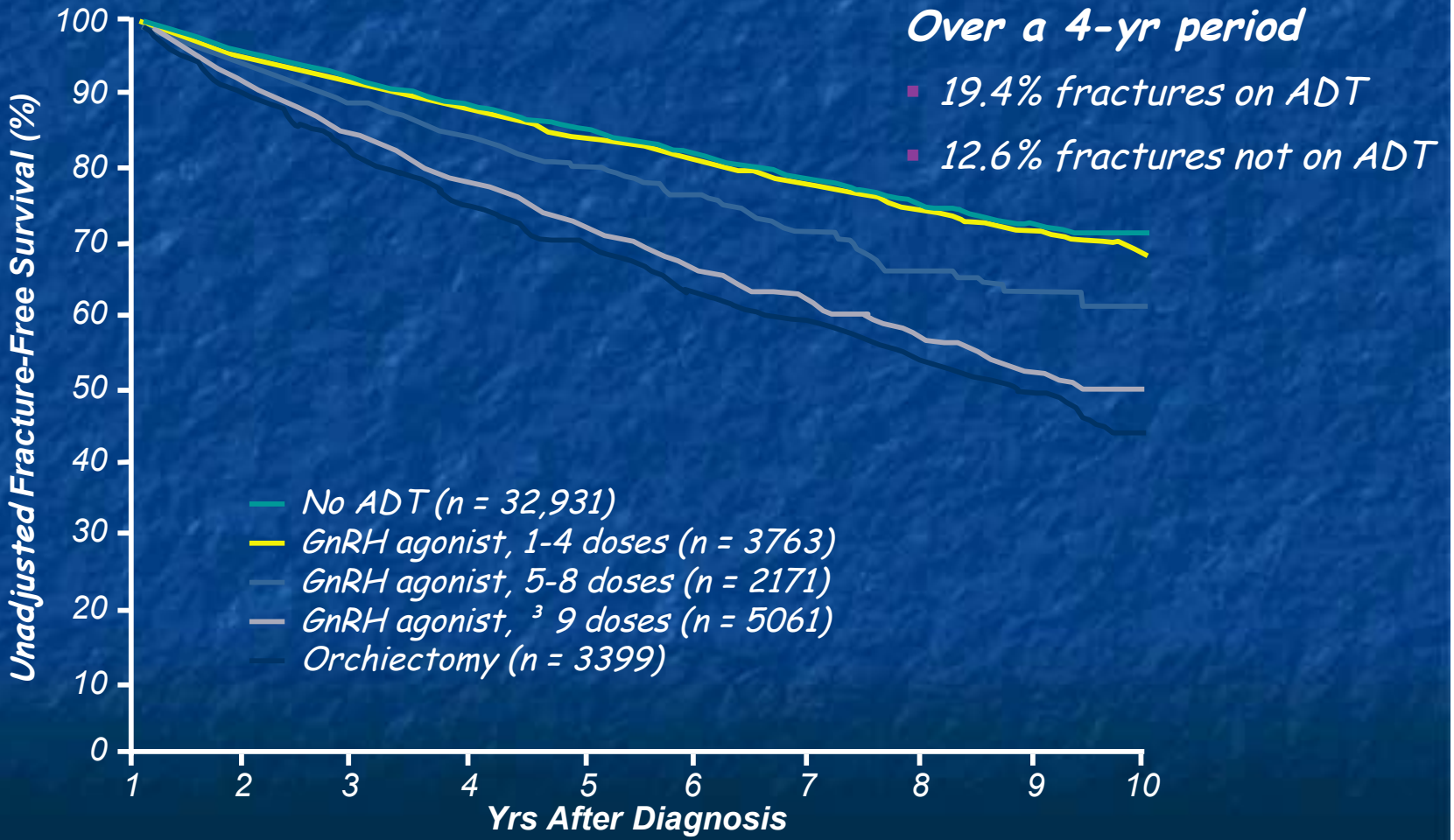
EMP = estramustine; HC = hydrocortisone; Pred = prednisone. [1]$p < 0.000$; [2]$p = 0.001$; [3]$p = 0.01$; [4]$p < 0.03$.

Ερωτήματα:

5) Χρειάζεται υποστηρικτική θεραπεία ο σκελετός και αν ΝΑΙ, ποιά;

- Οστική Απώλεια σε ασθενείς οι οποίοι λαμβάνουν ADT
- Πρόληψη των επιπλοκών που σχετίζονται με τον σκελετό σε ασθενείς οι οποίοι έχουν οστικές μεταστάσεις
- Πρόληψη των οστικών μεταστάσεων

Fracture-Free Survival Diminishes With Cumulative ADT Exposure



Shahinian VB, et al. N Engl J Med. 2005;352:154-164.

Denosumab Fracture Prevention Study

Current ADT for prostate cancer, 70 yrs of age or older or T score < -1.0 or history of osteoporotic fracture

(N = 1468)

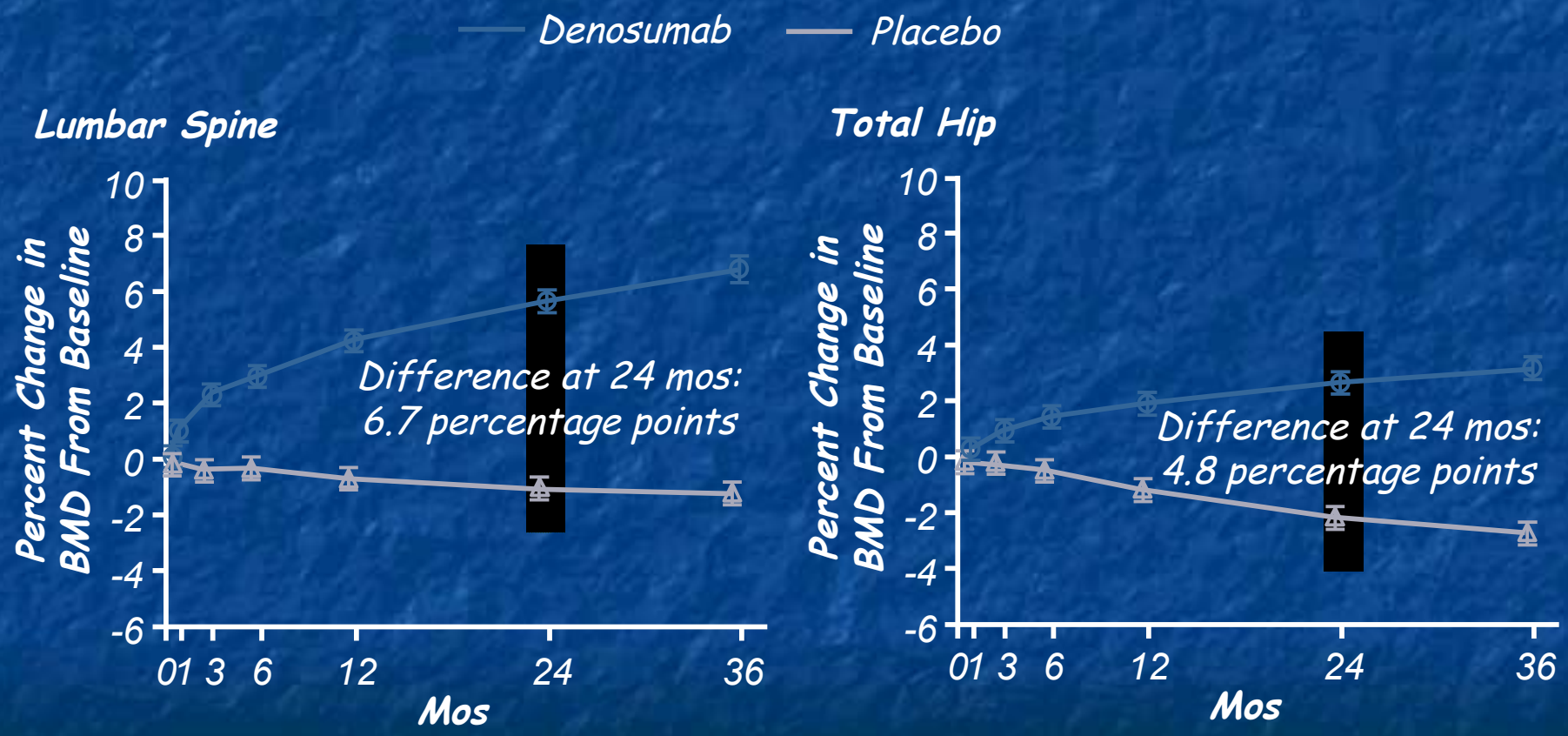
→ ***Denosumab** q6 mos for 3 yrs*

→ ***Placebo** q6 mos for 3 yrs*

- Primary endpoint: change in lumbar spine BMD
- Key secondary endpoint: new vertebral fractures

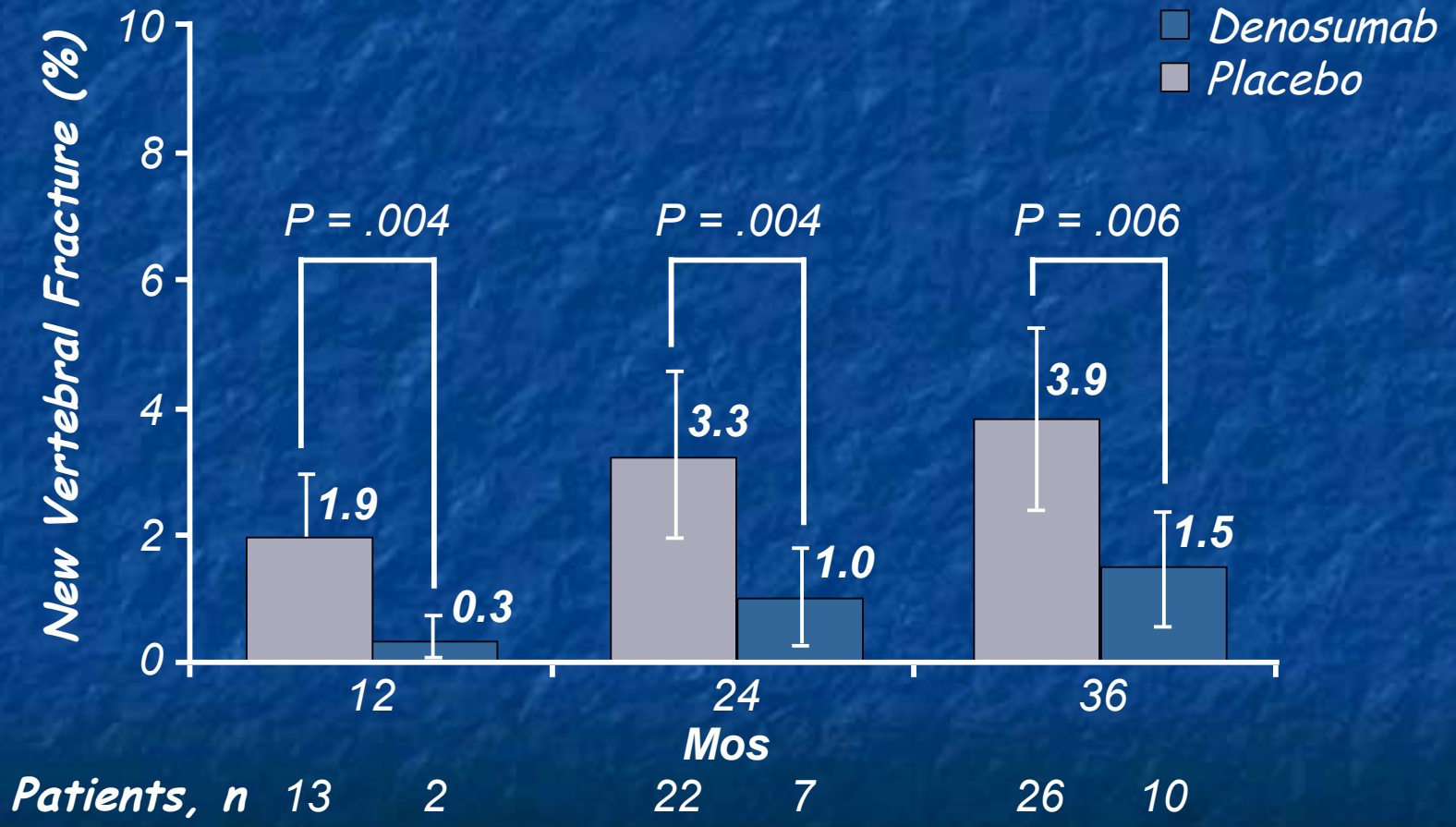
Smith MR, et al. N Engl J Med. 2009;361:745-755.

Denosumab for BMD Increase in Patients With Prostate Cancer Receiving ADT



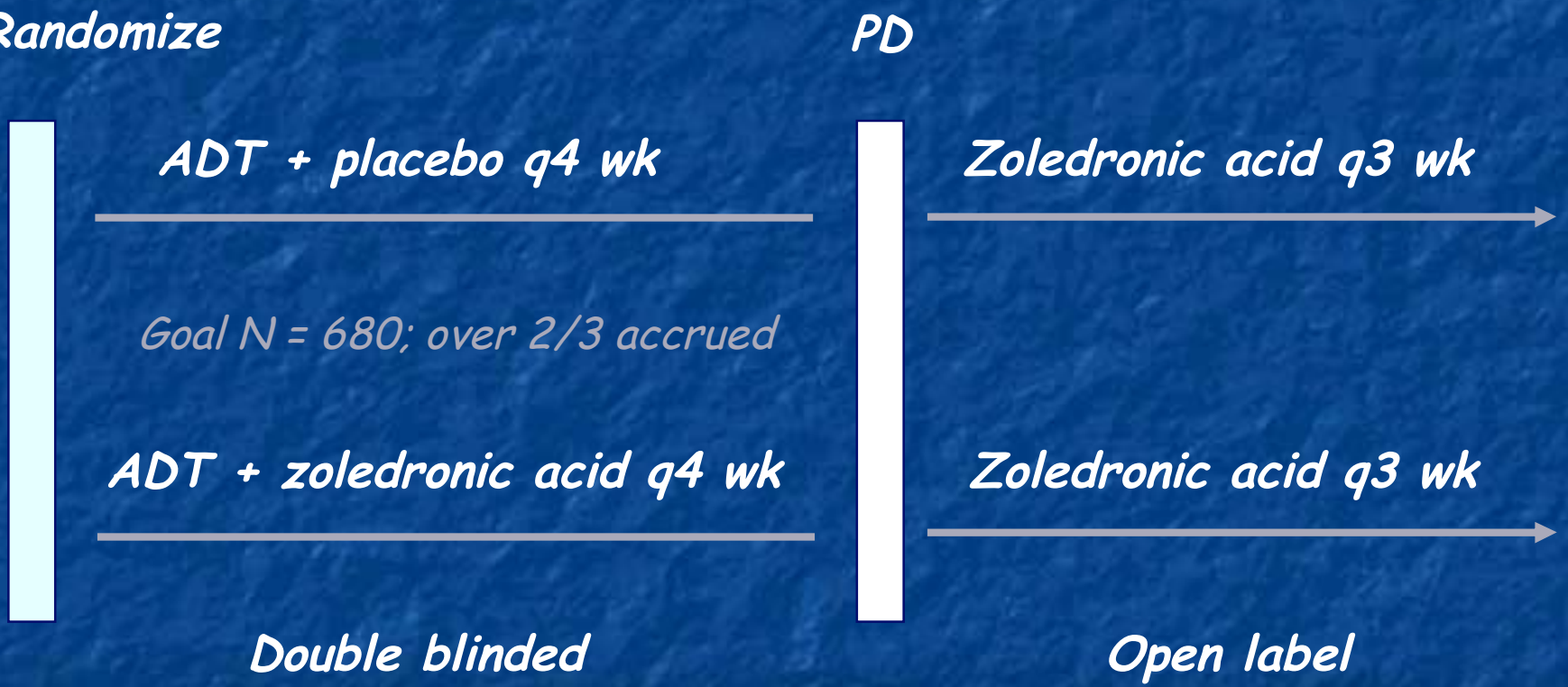
Smith MR, et al. N Engl J Med. 2009;361:745-755.

Denosumab for Fracture Prevention



Smith MR, et al. N Engl J Med. 2009;361:745-755.

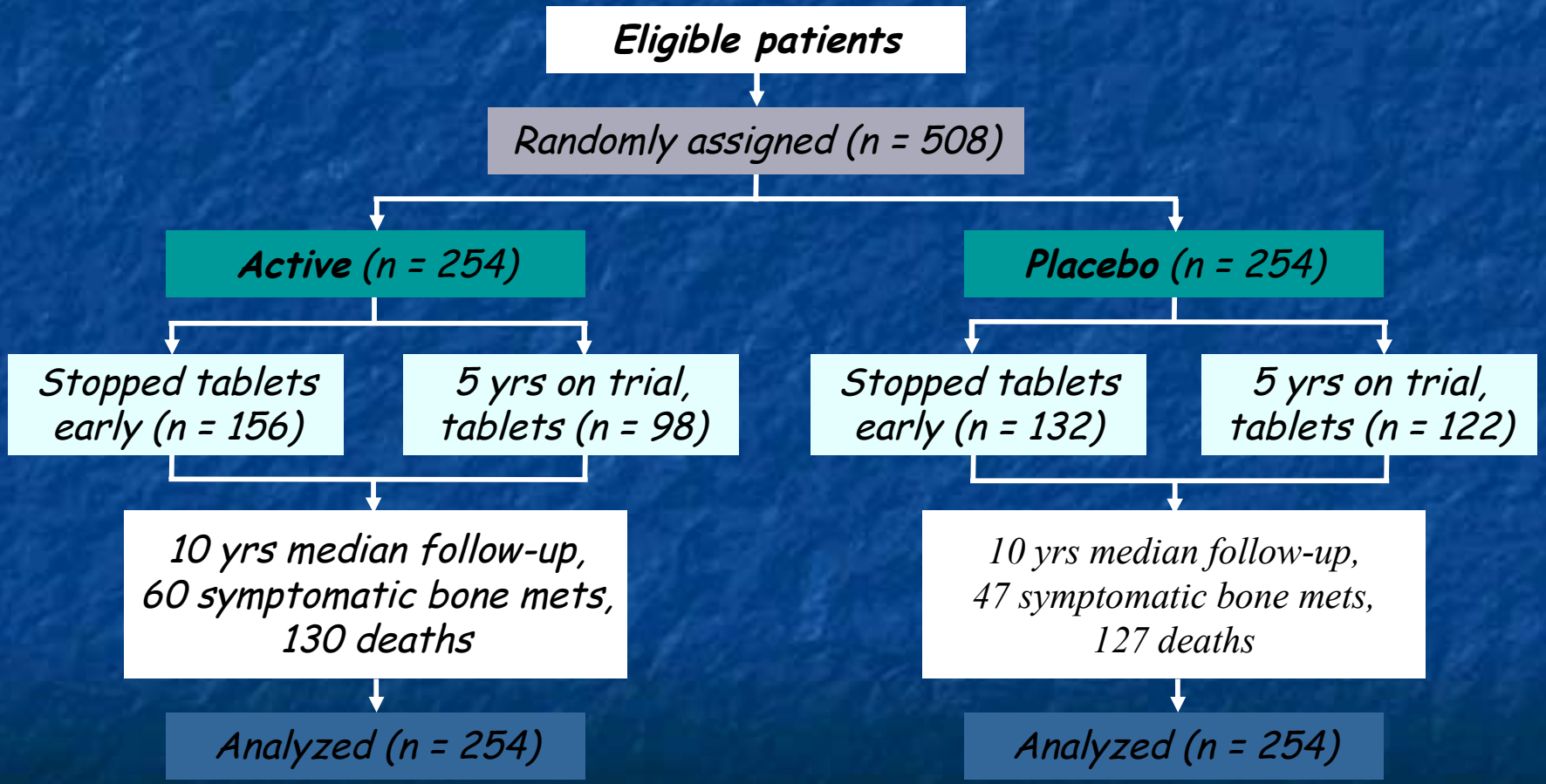
CALGB 90202: ZOL in Hormone-Sens Bone Mets Disease—No Current Proven Role



Primary endpoint: time to SRE; secondary endpoints: OS, toxicity

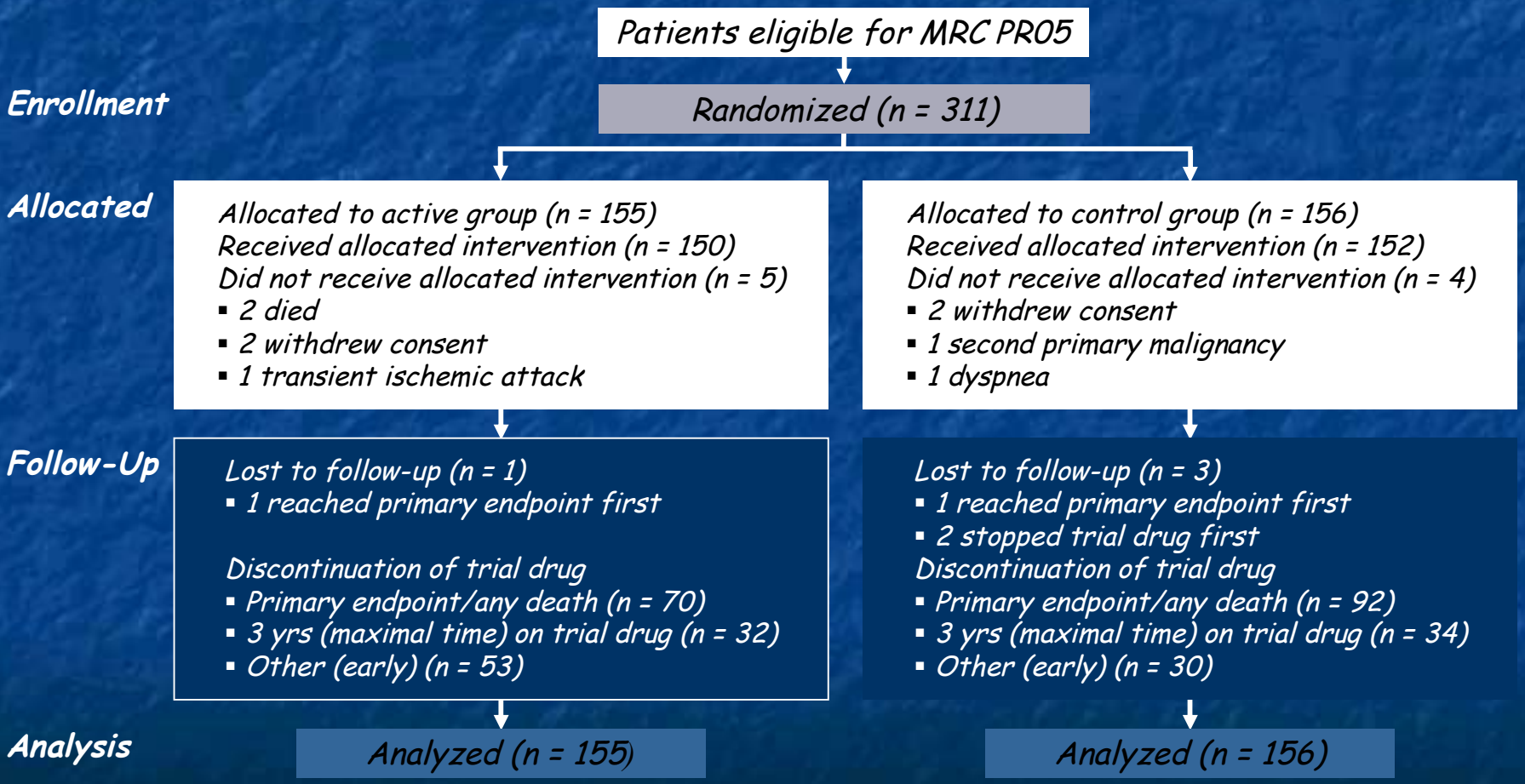
ClinicalTrials.gov. NCT00079001.

PR04: Clodronate in Nonmetastatic Patients; ADT Naive



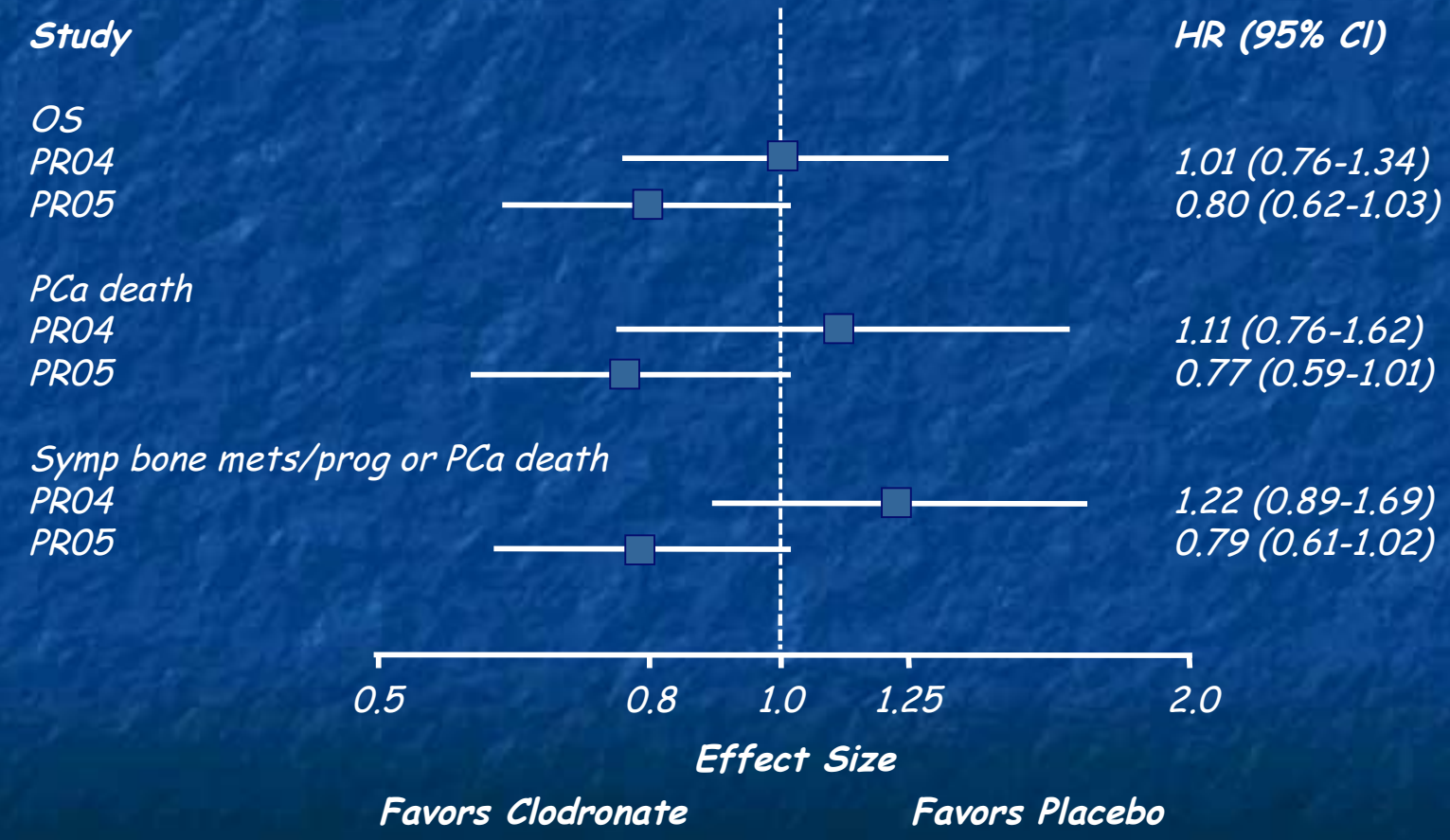
Mason MD, et al. J Natl Cancer Inst. 2007;99:765-776.

PR05: Clodronate in Bone Metastatic Patients on ADT



Dearnaley DP, et al. J Natl Cancer Inst. 2003;95:1300-1311.

Forest Plots: PR04 Compared With PR05



Mason MD, et al. J Natl Cancer Inst. 2007;99:765-776.

Do Bisphosphonates Prolong Survival?

- MRC PR05 study
  - Hormone-sensitive metastatic prostate cancer
  - Clodronate 2080 mg PO QD vs placebo
  - Endpoints
    - Primary: progression of symptomatic bone metastases or death
    - Secondary: OS, safety
- **PR05 overall survival *P* = .032 with early separation of curves**
- MRC PR04 no benefit in PSA-detectable-only disease

Dearnaley DP, et al. Lancet Oncol. 2009;10:872-876

12.9.3.1 Non-metastatic bone fractures

Androgen deprivation therapy increases the risk of non-metastatic bone fracture due to increased bone turnover and decreased BMD in a time-dependent manner, and there is an increased risk of fracture of up to 45% relative risk with long-term ADT (102). This is an important side-effect, as hip fractures in men are associated with a significant risk of death (103). Increased exercise, calcium and vitamin D supplementation are protective. Bicalutamide monotherapy could also be a bone-protective method based on a small, prospective, randomised trial, including 103 patients comparing bicalutamide, 150 mg/day, or medical castration (104) (LE: 1b).

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Bisphosphonates

Recently, bisphosphonates, such as pamidronate, alendronate or zoledronic acid, have been shown to increase BMD in the hip and spine by up to 7% in 1 year. The optimal regimen for zoledronic acid is unclear. One study recommends treatment every 3 weeks (105), while another trial has produced similar results with an annual injection (106). The optimal regimen is very important because of the risk of jaw necrosis, which may be both dose- and time-related (107). The initial BMD could be used to guide the choice of regimen (108). Thus, a 3-month injection might be given in osteoporotic patients for whom a yearly injection is likely to provide insufficient protection.

As previously observed in breast cancer, a significant benefit in OS has recently been demonstrated for biphosphonates in PCa, particularly oral first-generation clodronate versus placebo. After at least 10 years of follow-up, an absolute 8% increase in OS was observed at 8 years in a clodronate-treated group of PCa patients, who had an overall survival of 22% versus 14% in the placebo group (109). The benefit for OS applied only to M1 patients, but not to M0 patients. Although this is a post-hoc analysis and the results are surprising because clodronate has no bone protective effect in PCa, this study again highlights the potential impact of bone-targeted drugs and the need for continuous trials, e.g. the Zeus trial, which uses a more recent biphosphonate.

Denosumab

In 2009, a major advance in bone protection was made with the introduction of denosumab, a fully human monoclonal antibody against RANKL, which is a key mediator for osteoclast function, activation and survival. A total of 1,468 men with non-metastatic PCa receiving ADT were randomised to denosumab, 60 mg subcutaneous every 6 months, or placebo (110). The primary end-point was the percentage change in lumbar spine BMD at 2 years. Denosumab was associated with 5.6% increase in the lumbar BMD versus 1% decrease in the placebo arm. There were also significant BMD increases at the total hip, femoral neck and distal third of the radius. The vertebral fracture rate was less in the denosumab-treated group versus the placebo-treated group (1.5% vs 3.9%, p = 0.006). This benefit was similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, as the rates of adverse events were the same in both groups, without any jaw osteonecrosis or delayed healing in vertebral fractures. Denosumab may therefore represent a major advance in bone protection.

In addition, this drug has been shown to postpone bone metastases in non-metastatic patients in a large RCT of 1,432 patients (111). Denosumab, 120 mg every 4 weeks, increased the time to bone metastasis-free survival by 4.2 months compared to placebo, but was accompanied by the side effects of jaw necrosis in 5% of treated patients versus 0% in the placebo arm and hypocalcaemia in 2% of treated patients versus less than 1% in the placebo arm. However, the increase in bone metastasis-free survival had no impact on overall survival, which was 43.9 months in the denosumab group compared to 44.8 months in the placebo group. These results highlight the potential importance of targeting the bone microenvironment. However, the daily use of denosumab remains questionable because of related side effects and cost.

Lifestyle changes before starting long-term ADT

Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption and normalisation of their body mass index (BMI). A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry before starting long-term ADT. An initial low BMD (T-score > 2.5, or > 1 if other risk factors are present) indicates a high risk of subsequent non-metastatic fracture, suggesting the need for early preventive bisphosphonate therapy.

Obesity and sarcopenia

Obesity and sarcopenia are common and often occur early, during the first year of ADT. There is an expected increase in body fat mass by up to 10%, and a decrease in lean tissue mass by up to 3% (112). Both changes are linked to an increased risk of fracture.